UNIVERSITAT DE BARCELONA

Final Degree Project

**Biomedical Engineering Degree**

# Validation of the STN-DBS intervention as a treatment for Parkinson's disease by studying the accuracy of electrode placement and possible correlation with motor symptoms

Barcelona, June 2021


Author: Ilianne Guillot Vidal

Director: Dr. Jordi Rumià Arboix

Tutor: Agustí Gutiérrez Gálvez

# ACKNOWLEDGMENTS

This project would not have been a success if it had not been relied upon people from different professional fields, but who have dedicated all their time in helping and guiding me in every step. I would like to express my sincere gratitude for all those people who, by contributing a grain of sand or much more, have made it possible to get here today.

Firstly, I would like to thank a million times my director, Dr. Jordi Rumià, functional neurosurgeon at the Hospital Clínic of Barcelona, for everything he has done for me throughout this year. You have made this study lighter, and not only that, but you have made me fall even more in love with neurosurgery and neuromodulation, alongside opening me the doors to all the responsibilities a biomedical engineer has in this fast-paced world and in this specialisation, which has been my motivation from the beginning. I am very grateful for all the time you have invested in the study, together with believing in this project since its conception. It has been a great privilege working with you and most of all, learning from you.

I would also like to thank to all the team at the Neurosurgery department of the Hospital Clínic, for its hospitality and interest in my project; and to the chairman, Dr. Joaquim Enseñat, for listening me when I did not know what I wanted to do, and for guiding me in what study my engineering knowledge would best suit, as well as redirecting me to the department.

On the other hand, I would also like to express my gratitude to my tutor, Agustí Gutiérrez, which thanks to his more technical and physical knowledge has provided me with the necessary support and motivation to accomplish the analysis, guiding me in any step that I was stuck.

Last but not least, I would like to thank the unconditional support of my family and my friends. Not just for this project, but throughout the whole course of university. I couldn't have gotten this far without you by my side, you have been a must along the way. My most sincere thanks, always.

## ABSTRACT

Parkinson's disease is present approximately in 10 million individuals all over the world, being one of the most common neurodegenerative diseases, and statistics denote that its prevalence will raise in the coming years. Deep brain stimulation is an effective surgical treatment for patients who do not improve with drug treatment and who present many motor symptoms. Deep brain stimulation constitutes the implantation of electrodes in specific brain structures, nevertheless, this study has focused on the subthalamic nucleus, being the main target region for Parkinson's disease. In order to have satisfactory post-surgical results, where the patient has a considerable reduction in motor symptoms, it is essential to present a correct lead placement accuracy, which corresponds with what has been planned before surgery by terms of using the neuronavigator.

The principal objective of this study is to validate the accuracy of the actual technique used in the Hospital Clínic of Barcelona, which is guided exclusively by image, as well as to establish a possible relationship between the patient's clinic, following the UPDRS scale type III, once it has undergone surgery and the accuracy of the electrodes, to verify that it essential to achieve its maximum effectiveness. Thus, objective arguments of the image-guided and image-verified technique can also be given as well as providing assertion of completing the procedure with the patient completely anaesthetised, since currently in Catalonia most centres do so with the patient awake and with microelectrode recording.

A study has been performed on 74 patients operated on from 2015 to 2020 following the same methodology, where the AC-PC coordinates were acquired using Medtronic's StealthStation S8 navigator and the errors and statistical analysis were computed with MATLAB.

The average targeting accuracy found in the right hemisphere has been 1.923 mm ± 1.107 and in the left hemisphere of 2.364 mm ± 1.065, alongside the calculation of a Student t-test with a p-value of $1.384 \cdot 10^{-4}$. Furthermore, the majority of clinical results were very favourable, thus concluding that the protocol used in the Hospital Clínic is correct and alleviates the patient's anxiety.

## KEYWORDS

Parkinson's Disease · Deep brain stimulation · Accuracy · Targeting Accuracy · AC-PC coordinates · Neurosurgery · Motor symptomatology · Lead placement · Image-guided image-verified

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## GLOSSARY OF ABBREVIATIONS

**AC:** Anterior Commissure

**AC-PC**: Anterior Commissure - Posterior Commissure

**CT:** Computed Tomography

**DBS:** Deep Brain Stimulation

**F-DOPA:** 6-[F]-fluoro-L-dopa

**FDA:** Food and Drug Administration

**GPe:** External Globus Pallidus

**GPi:** Globus Pallidus Internus

**IPG:** Implantable Pulse Generator

**MER:** Microelectrode Recording

**mm:** Millimetres

**MRI:** Magnetic Resonance Imaging

**PC:** Posterior Commissure

**PD:** Parkinson's Disease

**PET:** Positron Emission Tomography

**SD:** Standard Deviation

**SEN:** Sociedad Española de Neurología

**SNc:** Substantia Nigra pars compacta

**SNr:** Substantia Nigra pars reticulata

**STN-DBS:** Bilateral Subthalamic Deep Brain Stimulation

**STN:** Subthalamic Nucleus

**T**: Tesla

**TE:** Targeting Accuracy

**VE:** Vector Error

**VIM:** Ventral Intermediate Nucleus

# INDEX

# 1. INTRODUCTION

## 1.1. MOTIVATION

Parkinson's disease (PD) is one of the most common neurodegenerative conditions affecting approximately 10 million individuals all over the world. Its cause it is still unknown, although it is believed that elements such as genetics and environmental factors could lead to the degeneration of neurons in specific brain regions which could arise the disorder. PD affects primarily elder people and, as life expectancy has increased significantly, statistics denote that in coming years PD's prevalence will raise. [1] [2]

PD combines many direct and indirect costs, including treatment, social assistance, psychology aid, among others. In Spain, the average annual expenditure may exceed 17.000€ per patient, whilst for the Ministry it reaches up to 2.5 million euros per year. As the disease severity progresses, an increase in costs is seen in tests, early retirements, hospitalisation, within others. In Spain, the 10% of PD patients present advanced Parkinson. [3]

The number of people affected by PD will be doubled in 20 years and will triple by 2050, stated by "*Sociedad Española de Neurología*" (SEN). [4] Moreover, the number of patients suffering from severe illness and presenting motor symptomatology which does not respond to drug treatment of levodopa will also risen.

Surgery is an effective treatment option for those patients whose medical treatment for tremor has been exhausted or whose symptoms of dyskinesia are profound. Deep brain stimulation (DBS) was first approved in 1997 as a therapy for PD's tremor, and in 2002 for advanced Parkinson's symptoms. Recently, in 2016, it was authorised for earlier stages of PD with motor symptoms not controlled by drug treatment. DBS comprises the insertion of electrodes in specific regions of the brain and an impulse generator battery is also implanted. It is one of the most important therapeutic advancements, although it is not suitable for all patients. [5] This study has focused on the subthalamic nucleus (STN), specifically the Bilateral Subthalamic Deep Brain Stimulation (STN-DBS) intervention by terms of acquiring the anterior commissure - posterior commissure (AC-PC) coordinates**.**

Lead placement accuracy is one of the most significant concepts to take into account when accomplishing a DBS procedure, as the target regions are situated deep inside the brain. The main motivation of this project is to accomplish a precision analysis in order to establish a possible clinical correlation with deviations.

## 1.2. OBJECTIVES

The main objectives proposed for this project are the following:

- **Validate** the accuracy of the implantation technique guided exclusively by image, which is the current methodology used in the Hospital Clínic for these interventions.
- **Establish** a possible relationship between Parkinson's disease symptomatology before and after being submitted to DBS surgery.
- **Provide** objective arguments for or against performing the surgery with the fully anaesthetised patient, alongside the image-guided and image-verified technique.

## 1.3. METHODOLOGY

The methodology of the project has been described in the workflow shown in Figure 1, and it is divided into two distinct groups.

The first one is focused on the imaging analysis, where the neuroimages, computed tomography (CT) and magnetic resonance imaging (MRI), of patients submitted to stereotactic surgery due to PD condition are assembled after a process of anonymization and codification to maintain patient privacy. Subsequently, a pre-processing is computed by terms of a coregistration of the post-implantation CT scan with the planning imaged fusion.

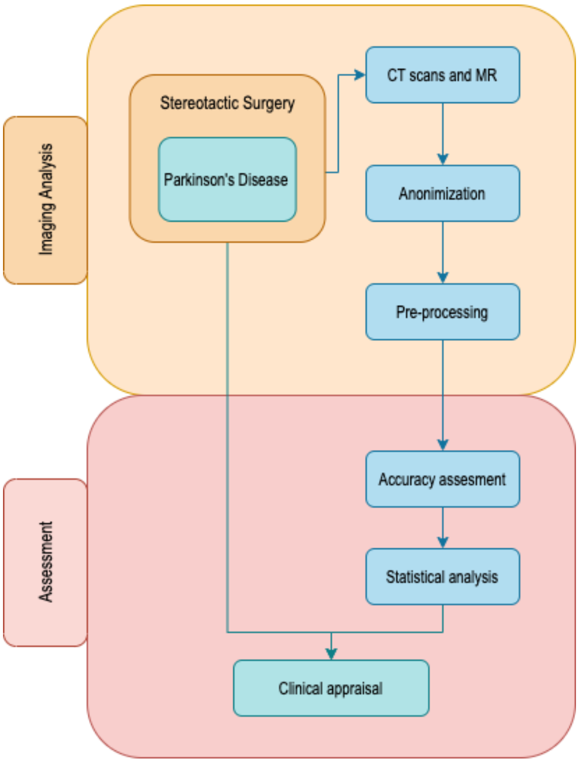


**Figure 1**. Methodology flow chart

The second group involves the assessment procedure, particularly the accuracy appraisal, and finally a statistical analysis in conjunction with a clinical analysis are performed.

The project is divided into 11 sections. Firstly, an introduction concerning the specific field is detailed, followed by the general theoretic background of Parkinson's disease as well as deep brain stimulation and error propagation. On section 3, a market analysis is precised and the different regulation followed during the project are shown in section 4. To mention all the programs available and used, the conception and detail engineering are fundamental. Additionally, detail engineering provides the project results and its analysis. Future research , as well as a general discussion, concerning DBS in PD is discussed in section 7. For the validation of the project, a technical and economic viability, as well as a particular project schedule are specified in section 8, 9 and 10.

## 1.4. SCOPE AND LIMITATIONS

Different limitations are present in all the study, as it is a bachelor's thesis and there is a set time to deliver the project and its final results. This project has been accomplished from September 2020 to June 2021, and it is important to emphasise that the data used during this work are included in a time between 2015 to 2020 since only those patients who have undergone the intervention through image-guided surgery have been encompassed. Thus, the number of patients is a limitation as the population of cases studied is less than 100. Also, not all patients who met this requirement presented all the images necessary to perform the data acquisition or the target was a different structure other than STN and have been rejected. Approximately 25 patients have been discarded for reasons similar to those mentioned above.

Furthermore, the study has consisted on the validation of the current technique, but a more complete study with an improvement of the approach and with the implementation of a real-time algorithm that detects the error during surgery could have been a great advance, however, due to time limitation it has not been possible to term.

The scope of this project included the following steps, always regarding and taking into account all the limitations disclosed earlier:

- Literature review and bibliographic research of current DBS techniques and future challenges.
- Analysis of different softwares such as Lead DBS and MATLAB to accomplish the assessment.
- Patient's data anonymization and co-registration of the preoperative MR image and the postoperative CT scan.
- Data acquirement of AC-PC coordinates of the STN target point for both cerebral hemispheres.
- Vector error assessment using MATLAB iterative loops.
- Statistical analysis including mean, standard deviation (SD) and a Student t-test performance.
- Discussion of the results and clinical relationship between them and the patient's symptomatology.

## 1.5. LOCATION OF THE PROJECT

The project data acquisition, including images, has been accomplished at the Neurosurgery room at the Fifth Floor, pavilion 6 of the Hospital Clínic of Barcelona. Furthermore, the coregistration and coordinates acquirements has been carried out in the Navigation Room, on the 8th scale of the 4th floor of the Hospital Clínic, which is the Neurosurgery department.

# 2. BACKGROUND

Before the analysis is realised and disputed, it is relevant to introduce general concepts which will be fundamental in order to understand the project. Additionally, the state-of-the-art technology in stereotactic surgery is analysed.

## 2.1. GENERAL CONCEPTS

General concepts such as a definition of Parkinson's Disease, Deep Brain Stimulation, including precision and accuracy as neuronavigation must be clarified.

### 2.1.1. PARKINSON'S DISEASE

Parkinson's Disease is present on a 1% of adults older than 60 years. PD is a neurodegenerative condition which affects nerve cells controlling movement, presenting a progressive worsening pattern. PD is mainly characterised by three cardinal features: tremors, muscular rigidity and bradykinesia (slowness of movement). Postural instability could also be an indication, somehow, many times it is presented as a non-specific one. PD has an effect on motor and on non-motor features, these last ones being anxiety, depression, autonomic dysfunction, sensory symptoms, within much others. [6]

PD is caused by the loss of dopamine-producing neurons in the substantia nigra, specifically the decreased of striatal 6-[F]-fluoro-L-dopa (F-DOPA). Dopamine is the neurotransmitter involved in motor skills, affecting the region of the brain regulating movement and balance. Nonetheless, dopamine is the prevailing neurotransmitter producing the motor symptoms, but other neurotransmitters are also implicated, causing non-motor symptomatology. [7] The primary indications of PD are a significant loss of dopamine as well as the presence of Lewy bodies, which are globs of the alpha-synuclein protein. [8]

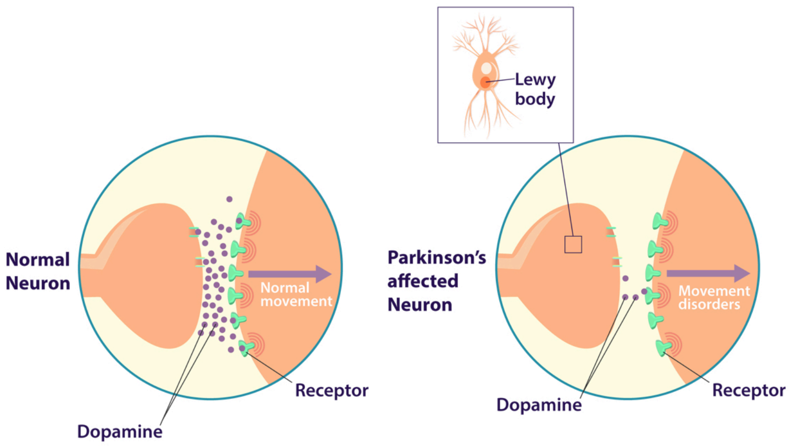


**Figure 2.** Normal Neuron vs Parkinson's affected Neuron [3]

Figure 2 shows how a Parkinson's affected neuron does not present as much dopamine as a normal neuron, leading to movement disorders. There is also the presence of Lewy bodies on the neuron affected by PD.

PD diagnosis is generally clinical, but it is difficult to diagnose as no specific test exists and symptoms could be common with other illnesses. Imaging could also be important to examine the anatomy and functioning of the patient's brain and other structures from the nervous system. Techniques used vary depending on the need, but these include:

- **Magnetic Resonance Imaging (MRI)**: Helpful in the detection of vascular Parkinsonism
- **Computerised Tomography (CT)**: Based on X-Rays being passed through the brain in order to compute cross-section pictures of the brain.
- **Positron Emission Tomography (PET)**: Mainly used in research as it is expensive and not always available. Quantifies the functional dopaminergic terminals in the striatum.
- **DaTSCAN™-SPECT**: Identifies the loss of dopamine-producing neurons.

Moreover, newly diagnose techniques are being researched such as blood or skin tests. [9]

There is no current therapy for PD, but some approaches such as medication or surgical interventions are able to slow down the symptomatology progression. Medication can be used as symptomatic treatment of motor and non-motor symptoms or as neuroprotection to slow down the disease progression.

Surgical options to relieve symptomatology of Parkinson's can be considered in those patient's whose medication is not able to show the desired results. Surgery is conditioned to improve only the motor symptoms such as tremors, which are initially treated with levodopa.

Years ago, surgery involved the demolish of specific structures of the brain implicated with motor symptoms including the globus pallidus, the thalamus or the subthalamus. These procedures involve a high probability of death, within other significant risks. Currently, **deep brain stimulation** (DBS) is the most common surgery for alleviating PD symptoms. [10]

The Unified Parkinson's Disease Rating Scale (UPDRS) is a scale developed in order to follow a longitudinal course of PD providing a comprehensive and efficient mean to monitor the advancement of the condition. The four sub-components regarding the UPDRS are Part I (mentation and behaviour), Part II (evaluation of daily-life activities), Part III (motor evaluation) and Part IV (therapy complications). This study is focused on Part III of the UPDRS. [11]

### 2.1.2. DEEP BRAIN STIMULATION

Functional neurosurgery is a minimally invasive surgery based on medical images which focuses on functional localisations of the brain with the aim of treating different movement-related disorders, pain and epilepsy. Stereotactic neurosurgery assigns three cartesian coordinates (x, y and z) to each point of the encephal which are correlated to the preoperative planning image, mostly MRI, and the actual space of the patient's brain at the operating room. It is considerably important to define the coordinates of the stereotactic target as also the trajectory it will follow. Reasons are that the encephal is highly vascularised and also, the surgeon must be able to introduce surgical instruments accurately avoiding dangerous structures. [12]

Deep brain stimulation consists of a procedure where a device is implanted to the patient with the aim to deliver programmed electrical pulses and modulate the activity of target neurons which are located deep in the brain, to decrease motor symptoms. This electric current changes the extracellular potential of cells and fibres located nearby the electrode. The main DBS lead target in PD is the STN, but some other targets could include the globus pallidus internus (GPi) and the ventral intermediate nucleus (VIM). This lead is connected to a subcutaneous implantable pulse generator (IPG) located under the skin of the anterior chest wall, containing battery and stimulation hardware. The pulse generator is connected to a connecting wire which is tunnelled from the chest to the skull, where the lead is. [13] [14] Figure 3 displays how the electrode and the generator are placed, and how stimulation occurs in the GPi or STN shown in a sagittal cut.

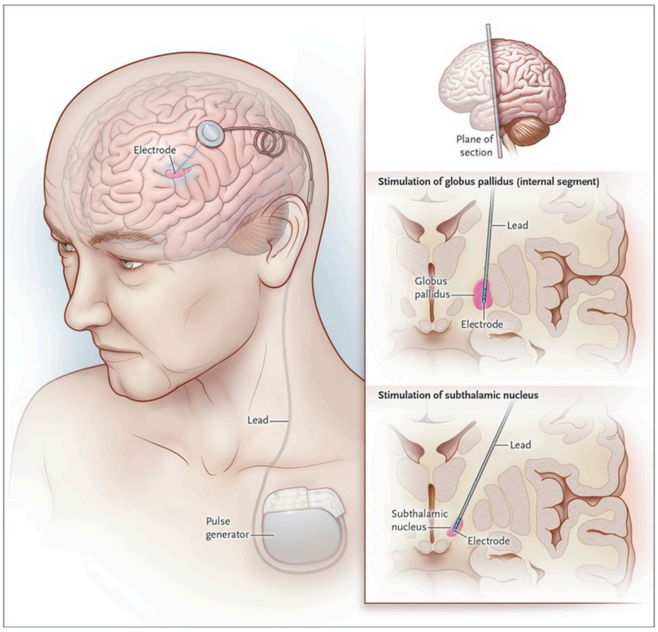


**Figure 3**. Implantable DBS: Electrode, lead and pulse generator [13]

Once the implantation is fulfilled, a clinician configures the IPG parameters in order to optimise therapy and obtain better results treating the symptomatology. Normally stimulation is based on a high-frequency (60-185Hz), continuous and biphasic pulse train presenting amplitudes from 0 to

10 V and pulse widths between 60 and 450 μs. Electrode implantation can be lateral or bilateral and stimulation is applied along the DBS lead. [14]

DBS is indicated for those patients suffering Parkinson's for four years or more and who do not always present a response to their medication, or those patients with dyskinesia. The reason is that DBS helps to decrease motor symptomatology; mainly the three cardinal features. This surgical intervention is not indicated for people suffering from dementia as DBS could worsen cognition or memory. [15]

Precision and accuracy are fundamental concepts in order to proceed to a DBS implantation. Different strategies, both anatomical and functional, must be used to confirm the correct placement of the electrodes. Intraoperative imaging and computer software support such as neuronavigation allows surgeons to know where the electrodes are implanted. Neuronavigation provides an interactive correspondence between imaging studies and the surgical field thanks to the co-registration of virtual images with the material volume of the patient. Co-registration is mainly achieved by establishing common points known as fiducials which must be visible in both the images and the patient, or sometimes by the registration on a stereotactic frame which is mounted on the patient's head. A functional strategy would be to keep the patient awake during surgery.

### 2.1.3. PRECISION AND ACCURACY AND PROPAGATION OF UNCERTAINTY

*Precision and Accuracy*

Accuracy is the proximity between the result of the measure and the real value, whilst precision is the spread of the measures, the closeness of measurements within each other. Accuracy is a description of systematic errors whereas precision is representation of random errors.

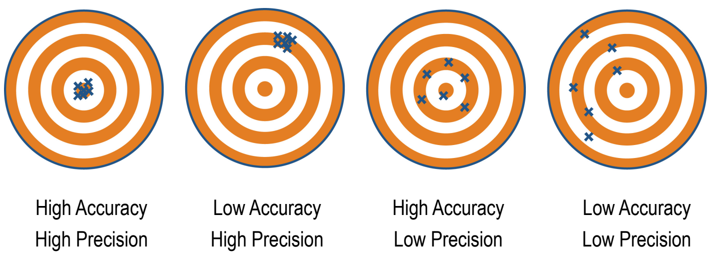


**Figure 4.** Accuracy vs Precision [16]

Figure 4 displays the main differences between the two static characteristics: accuracy and precision. As it can be seen, the best combination is a high accuracy and high precision.

*Propagation of uncertainty*

Error transmission in statistics is the effect of distinct random errors which propagate through each other. Regarding the DBS intervention situation, three different architectures for the electrode implantation could be described depending on the system followed: frame-based operation, frameless operation or iMRI Guided operation. Throughout the process, errors are dragged on with each step and, although at first it could be a very small error, as it is dragged and accumulated, it ends up being a significant error.

In frame-based operations, which is the current technique followed in the Hospital Clínic to accomplish the electrode implantation, different errors could appear and could propagate during the whole process and they are reviewed in Figure 5. Firstly, when registering CT and MRI images, there may be technical or image fusion errors. In the registration and planning process, technical errors as well as human errors could appear. Finally, when proceeding in the surgical intervention to the burr hole opening a brain shift error exists as well as in the electrode implantation, mechanical and human error could be present. Finally, in electrode fixation the lead migration error is a possibility. Once all the process is fulfilled, the targeting error is achieved. [17]

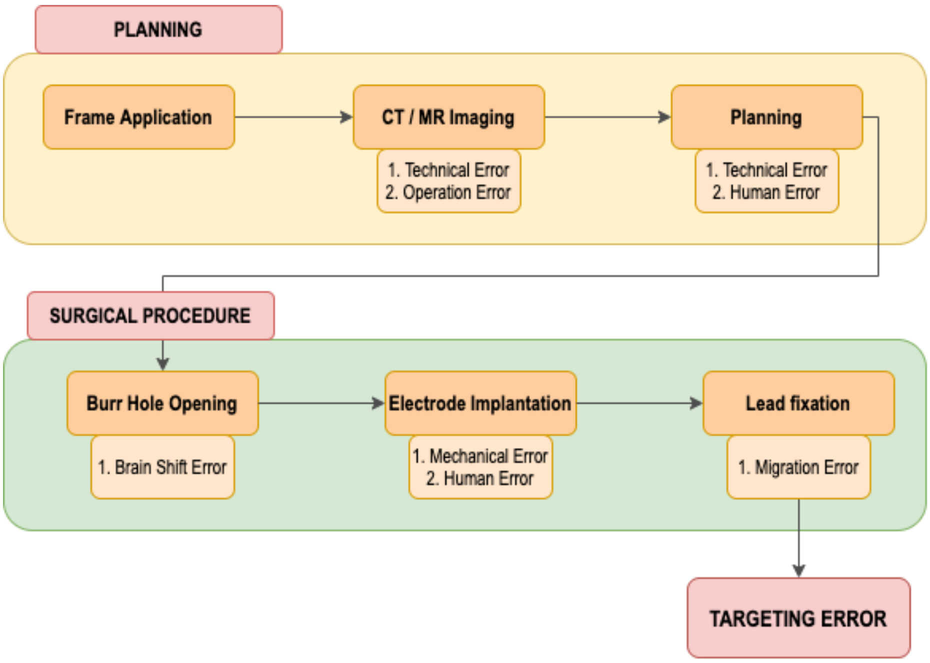


**Figure 5.** Propagation of uncertainty in the implantation of DBS electrodes in a frame-based

## 2.2. STATE OF THE ART TECHNOLOGY

DBS is a precise method of neuromodulation technology which was certified as a medical treatment of medication-refractory PD by the Food and Drug Administration (FDA) in 1997. This evidences that DBS is a recent technology implemented in neurosurgery. Hence, DBS is a rapidly-growing area of endeavour. DBS technology has been developed from cardiac pacemakers.

On 1950, the insight of neuromodulation using high-frequency and pulsatile stimulation for PD therapy was firstly detailed by Hassler; where patients affected by Parkinsonism were stimulated by wires inserted in the GPi. Hassler brought to a close that high-frequency stimulation, on the range of 25-100 Hz relieved tremor. Since that moment, over 100.000 patients worldwide have been conducted implantation with DBS systems, notwithstanding, the mechanism is still a matter of debate in both medical and research fields. [18] Lawrence Pool, a neurosurgeon from Columbia University, is known to be the first implanting an electrode, specifically in a woman with depression and anorexia. [19]

DBS is nowadays being implemented as a treatment in a wide range of disorders, including epilepsy, dystonia, and severe obsessive-compulsive disorder. The aforementioned clinical applications might differ during the following years as many clinical trials are testing efficacy and safety of DBS on other pathologies like severe treatment-refractory major depressive disorder, depression, delaying Alzheimer's disease and chronic pain.

*Electrode configuration and stimulation*

*Configuration.* Electrodes used in deep brain stimulation techniques depict different configurations and stimulations. With reference to the common DBS electrode configuration, which emerged on 2002, the conventional quadripolar electrode has four stimulating contact at the tip of the probe. This cylindrical configuration may produce a spherical electrical field shaped along the z axis of the lead, and it may spread outside the desired target producing side effects.

In 2015, directional leads appeared and allowed a directional steering and control of the electrical field, reducing the possible adverse effects as it enhanced the therapeutic window. Directional leads, instead of presenting a cylindrical configuration, uses radially segmented contacts. Finally, the eight lead contact electrode with multiple independent current control, which has the ability of having different stimulation parameters in each electrode contact. [19] [20] The different type of configurations can be observed in Figure 6.

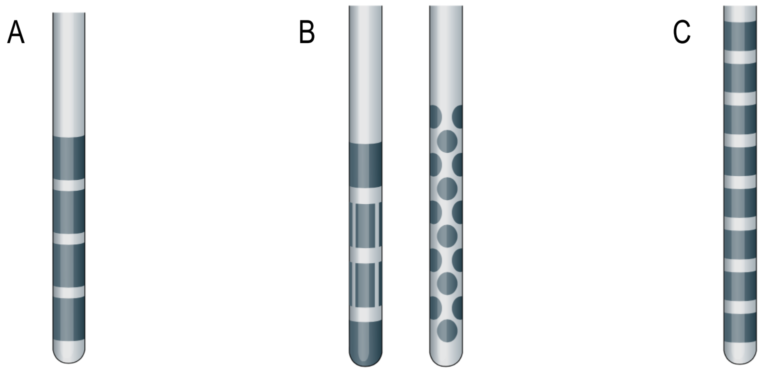


**Figure 6.** Deep brain stimulation electrode configurations [17] **(A)** Conventional quadripolar electrode. **(B)** Directional DBS electrode. **(C)** Eight contact electrode

*Stimulation.* Depending on the DBS electrode configuration proposed, stimulation can vary (Figure 7). Firstly, in the conventional quadripolar electrode, a unipolar or bipolar stimulation could be computed, as well as an interleaving stimulation. In the case of a unipolar stimulation, the current will be directed from the battery to one electrode contact, or conversely with a rapid alternating. With respect to bipolar stimulation, the current will be flowing from between the different electrode contacts, one acting as an anode and the other as a cathode. Finally, in an interleaving stimulation the current is alternated with different stimulation configurations.

Concerning directional DBS electrodes, the current can be directly targeted or shaped depending on clinical symptoms or anatomy. Lastly, referring to an eight contact electrode configuration, the multiple level stimulation is applied, allowing different neural targets to be stimulated across the electrode trajectory.

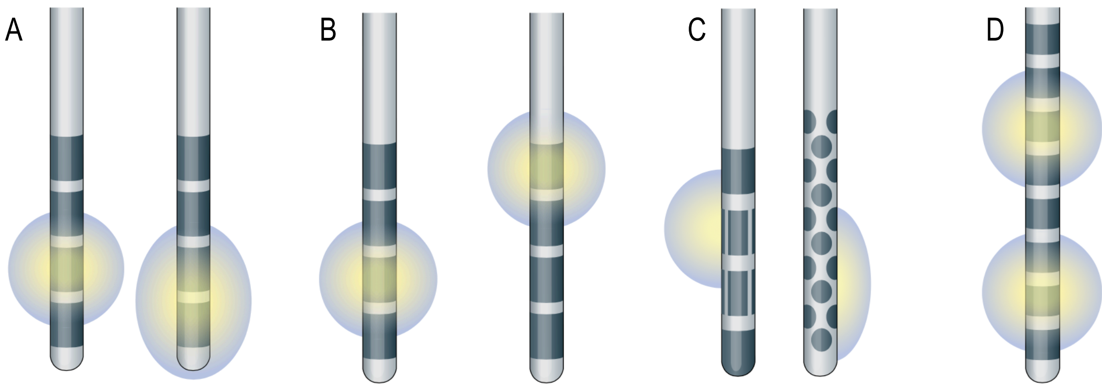


**Figure 7.** DBS electrode types of stimulation [17] **(A)** Unipolar and bipolar stimulation. **(B)** Interleaving stimulation. **(C)** Directional stimulation. **(D)** Multiple level stimulation

*Innovation in electrode and IPG design*

Future challenges comprising the DBS field entails research for physiologists, engineers and clinicians. In Table 1, one can observe the main improvements DBS could suffer on the following decades, determined by if they are affecting the electrode or the neurostimulator.

| **FUTURE CHALLENGES** | |
|---|---|
| **ELECTRODE** | New targets for stimulation |
| | Patient-specific Modeling |
| | Current Steering |
| **NEUROSTIMULATOR** | Current controlled stimulation |
| | Adaptive DBS and closed-loop algorithms |
| | Rechargeable battery |
| **NON-INVASIVE DBS** | Temporally interfering electric frields |
| | Low intensity pulsed ultrasound |

**Table 1.** Future challenges involving DBS

*Electrode improvements*. Thorough the upcoming years, software and hardware DBS system and implantable devices will need adjustment. One of the most considerable improvements that could occur is to ameliorate the targeting accuracy of the DBS lead and to enable a larger amount of patient-specific modelling of the electrical field within the patient's brain, as DBS electrodes are frequently positioned adjoining important functional brain structures and the outcomes of the electrical field ejected could cause numerous side effects.

Target accuracy is fundamental in DBS procedures, alongside enhancement in high-technology imaging, which could manage to directly image small nuclei and subnuclei (main targets), helping localisation. [21]

A further electrode improvement could be the inclusion of DBS leads containing radially-segmented or multi-prong electrodes, which have the capacity of generating a more precise electric field around the DBS lead. [21] Electrode design is fundamental in terms of innovation of DBS. Currently, the most used DBS electrodes present a quadripolar configuration, four equally space contacts at the tip of the probe. A quadripolar configuration allows the electric field to be shaped along the *z* axis, whilst in 2015 directional electrodes appeared presenting a more versatile shaping of the electric field. Electrode wires are made of platinum-iridium connectors of nickel alloy are encased in a polyurethane sheath. [19]

*IPGs improvements.* Moving onto the neurostimulator improvements, closed-loop strategies could provide the patient with a more stabilised therapy by programming the IPG. The search of biomarkers is fundamental in order to achieve a close-loop, as DBS must be able to feed the information back into a control algorithm. In PD, the biomarker is thought to be a beta-band activity (13-35 Hz) present in the STN since the signal is abolished by dopaminergic and DBS therapies.

The introduction of rechargeable batteries would be also an improvement as revision surgeries for replacing IPG would be reduced, although they would not be completely eliminated. Rechargeable batteries include an increase in technologies such as complex software algorithms. Rechargeable batteries would cause a great save in a patient undergoing a chronic DBS therapy, as the cost of an IPG ranges between $12.500 and $26.000. Another way of reducing associated costs with DBS therapy is to improve the outcome of the treatment and reduce surgery complications, which could be an infection, accuracy errors, within others. [21]

Figure 8 exhibits, in a comparative graphical representation, the main differences between the current DBS system available (8.a.) and the predicted DBS system (8.b.) regarding the introduction of some innovation which has been specified beforehand.

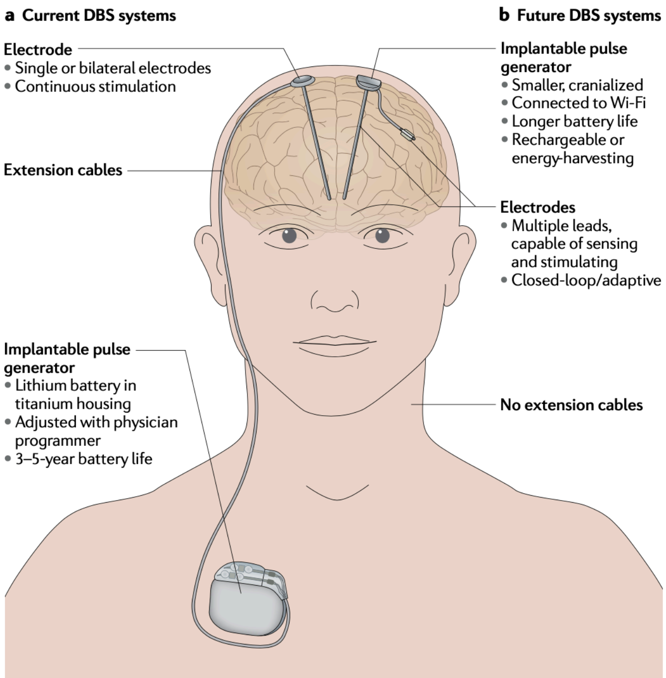


**Figure 8.** (a) Current DBS system compared with a (b) predicted DBS system [19]

*Future Challenges*

Despite all the improvements mentioned beforehand, one of the main challenges which have been recently studied by the Massachusetts Institute of Technology and the Harvard Medical School is accomplishing a noninvasive methodology of DBS by non-implanted electrodes placed on the scalp. [21] Currently, these experimental studies have been taken place in mouse models. This approach could transform the procedure to a noninvasive one, reducing possible risks and being more accessible to patients as the cost would also be reduced. In this specific study, two high-frequency electrical currents are generated using electrodes in the scalp, that they differ by a very small amount: one frequency of 2.0kHz whilst the other is of 2.01kHz. Both frequencies have a receiver and an emitter electrode. These high-frequencies lead to neurons not being able to fire action potentials, but their currents will interfere with one another and they will finally generate a small region of low-frequency current (in this specific case, of 0.01 kHz) deep in the brain that neurons are able to follow, hence the high-frequency is cancelled (Figure 9). [23] [24]

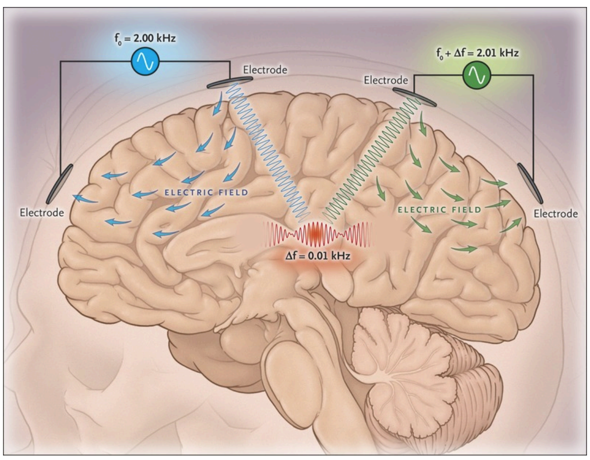


**Figure 9.** Possible non-invasive DBS stimulation [23]

Other studies carried out by Hui Zhou et al, from the University of Chinese Academy of Sciences, have concluded that noninvasive ultrasound DBS is able to treat PD in mice. Ultrasounds are mechanical waves with the ability to evoke neural activity, and low-intensity pulsed ultrasound finally showed the capacity of enhancing motor function in a mouse model. [25]

*DBS Stereotactic systems*

For DBS implantation, different stereotactic systems can be used. These systems can be classified into three main groups, frame-based, frameless and the iMRI-guided systems (Table 2).

The gold standard apparatus in functional neurosurgical interventions from decades has been the **frame-based stereotactic system**, based on a frame which fixes the patient's head and it is coupled with navigation software. Frame-based stereotaxis includes the Leksell system (Elekta Instruments Inc., Sweden), the Zamorano-Dujovny system (Stryker-Leibinger Inc., Germany), the Riechert-Mundinger system (Inomed Pte Ltd., Germany), the Cosman-Roberts-Well system (Radionics Inc., USA), Sugita system (Mihuzo Medical Co Ltd., USA) and the Neuromate robot (Renishaw Inc., UK).

| STEREOTACTIC SYSTEMS | | | |
|---|---|---|---|
| | **MODEL** | **ENTERPRISE** | **COUNTRY** |
| **FRAME-BASED SYSTEM** | Leksell | Elekta Instruments Inc. | Sweden |
| | Zamorano-Dujovny | Stryker-Leibinger Inc. | Germany |
| | Riechert-Mundinger | Inomed Pte Ltd. | Germany |
| | Cosman-Roberts-Well | Radionics Inc. | United States |
| | Sugita | Mihuzo Medical Co Ltd. | United States |
| | Neuromate robot | Renishaw Inc. | United Kingdom |
| **FRAMELESS SYSTEM** | NexFrame | Image-Guided Neurologics Inc. | United States |
| | STarFix microTargeting Plaform | FHC Inc. | United States |
| | Stealth Autoguide | Medtronic Inc. | Ireland |
| **iMRI GUIDED SYSTEM** | ClearPoint SmartFrame | MRI Interventions Inc. | United States |

**Table 2.** Model and enterprise of the three stereotactic systems available

Nonetheless, the use of **frameless systems** has increased over time. Frameless systems include NexFrame (Image-Guided Neurologics Inc., USA), the STarFix microTargeting Platform (FHC Inc., USA) and the Stealth Autoguide (Medtronic Inc., Ireland). Finally, **iMRI-guided systems**, in this case, ClearPoint SmartFrame (MRI Interventions Inc., USA) have also been gaining ground in recent years.

Some of the lasts stereotactic systems introduced in the market where the Neuromate robot and the ClearPoint SmartFrame, making DBS implantation a more complex procedure but presenting better targeting accuracy (TE). [21] The Neuromate robot (Figure 10) is a robotic arm with five degrees-of-freedom which is coupled into a personal computer-based kinematic positioning Software system. [26] [27]

ClearPoint SmartFrame (Figure 11) is based on real-time MRI guidance as a minimally invasive procedure during implantation or for surgical planning. [28] This system uses a SmartFrame trajectory device which enables the MRI-guided alignment and implantation of the depth electrodes. ClearPoint is also assembled into specific software with the aim of guiding the physician.

**Figure 10.** Neuromate robot involved in surgery planning (right), assembled software system (left) [27]

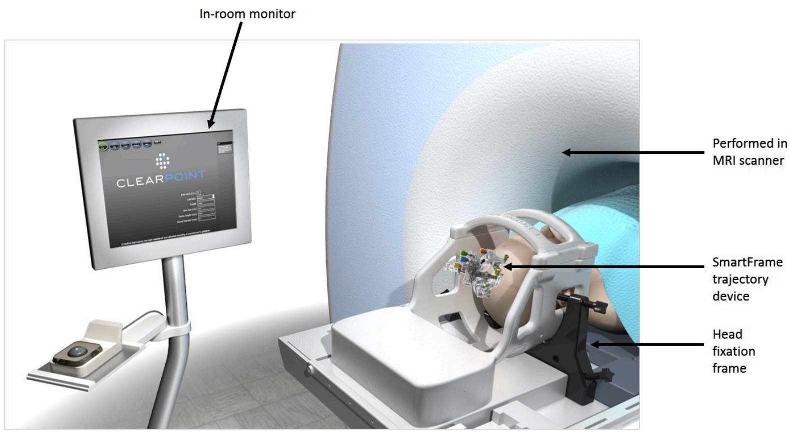


**Figure 11.** ClearPoint SmartFrame architect [28]

The founded TE in the Neuromate Robot has been of 0.86 ± 0.32 millimetres (mm), whereas the iMRI-guided system showed a TE of 0.6 mm. In the Leksell stereotaxis system, reviews have found out a TE varying of 3.00 mm to 1.3 mm. Similar results have been found in frameless systems. Nonetheless, neurosurgeon's proficiency and expertise in DBS implantation, different usage of peripheral equipment and devices and the hospital could make the TE fluctuate. [17]


**Figure 12.** Stealth Autoguide robot coupled with navigation [29]

Finally, Stealth Autoguide cranial robotic (Figure 12) assures continuous real-time visualisation as well as a high precision in stereotactic surgery. One of the main characteristics is that it presents feedback and robotically-assisted movements which allow the surgeon to align quickly and accurately the surgical plans for the procedure. [29]

In stereotactic surgery, neuronavigation (both hardware and software) is coupled with surgical planning and with the procedure. Neurosurgeons at the Hospital Clínic work with the StealthStation™ S8 Surgical Navigation (Medtronic Inc., Ireland). Procedures are achieved with frame-based systems (Leksell) and with Stealth Autoguide.

In stereotactic surgery, it is considerably important the use of intraoperative image, such as MR and CT. In stereotactic procedures, CT images assure the proper placement of the leads in the STN or other targets. O-Arm Surgical Imaging (Medtronic Inc., Ireland) is a mobile CT system which is intraoperative 2D or 3D imaging system integrated in the operating room used in Hospital Clínic. [30]

# 3. MARKET ANALYSIS

## 3.1. MARKET SECTOR

The market sector contemplated in this project is the one related to deep brain stimulation technology as well as neuroimaging. Consequently, the different major brands focused on neuromodulation are detailed and described below. Neuromodulation is defined as the alteration of nervous activity by targeting a stimulus in a specific nervous structure and is comprised by non-invasive methods as well as invasive methods, which are differentiated depending on the type of stimulus performed: electrical or magnetic. In this project, the relevant neuromodulation procedure is deep brain stimulation, being an invasive technique by terms of applying an electrical stimulus to the desired target. [31] The three main companies are Boston Scientific Corporation (Marlborough, MA, USA)), Medtronic Inc. (Dublin, Ireland) and Abbott Laboratories (Abbott Park, IL, USA), and their principal products are specified underneath.

Boston Scientific Corporation presents all the devices needed to perform deep brain stimulation, such as electrodes and accessories, the neurostimulator and a software planner (*GuideTM DBS Simulation*) using pre-operative MR images and post-operative CT and they all are categorised by the name VerciseTM. [32] Regarding the *VerciseTM DBS Lead*, it presents an eight ring contact lead with multilumen tubing and filar conductor cables inside, whilst the *Vercise CartesiaTM Directional Lead* is characterised by eight contacts configured into two ring electrodes and two 3-segment electrodes, as well as a radio-opaque marker, which is mentioned in the product detail description. [33]

**Figure 13.** (a) Boston Scientific VerciseTM DBS Lead. (b) Boston Scientific Vercise CartesiaTM Directional Lead [33]

Figure 13 displays the main differences between the VerciseTM DBS Lead (13.a) and the Vercise CartesiaTM Directional Lead (13.b). The principal distinction between them is that DBS lead has a linear eight contact lead, and the Directional Lead has one dome tip contact, six segmented contacts and finally one ring contact. Nevertheless, they are both composed by polyurethane in the outer jacket tubing, acting as an insulator, and of platinum or iridium in contact material as these materials present a minimal toxicity as well as being conductive.

Regarding Medtronic Inc., the PerceptTM PC Neurostimulator is used in DBS for PD. [34] Different models of brain neurostimulation leads exist, specifically the Medtronic 3387 (standard electrode spacing), Medtronic 3389, which is the compact electrode spacing and the mostly used and lastly Medtronic 3391, comprising large electrodes and wide spacing. [35] [36]

Medtronic Inc. also has commercially available surgical imaging systems which are essential to ensure a good outcome of surgery. The *O-arm™* system constitutes of an intraoperative two-dimensional fluoroscopic and three-dimensional imaging system. It is compatible with the Software StealthStation™ navigation, and it's main advantage is that it ejects the require to send the patient to the hospital radiology centre. [30]

Finally, St. Jude Medical (Minnesota, USA), later acquired by Abbott Laboratories (Illinois, USA), was the first medical company to develop a constant current device for deep brain stimulation. The DBS leads from St. Jude / Abbott are the Infinity DBS lead which are characterised for having 4-contact quadripolar electrodes (*Infinity 4-channel lead 6166 & 6168* and *Infinity 4-channel lead 6167 & 6169*) and 8-contact directional electrodes (*Infinity directional lead 6170 & 6172* and *Infinity directional lead 6171 & 6173*). The Abbott Infinity IPGs present compatibility with Medtronic DBS leads. It is important to emphasise that the Abbott Infinity DBS leads are not MRI-compatible. The diameter and contact spacing depend directly on the model. [36] The Abbott's Infinity DBS System is the first wireless iOS software mobile platform offering a personalised treatment minimising adverse effects. [37]

Table 3 comprises the main physical difference between the different DBS electrode models precise beforehand of the three main enterprises.

| DEEP BRAIN STIMULATION ELECTRODES | | |
|---|---|---|
| **Boston Scientific** |  | Vercise™ Linear 8-Contact Lead |
| |  | Vercise Cartesia™ Directional Lead |
| **Medtronic** |  | Medtronic 3387 |
| |  | Medtronic 3389 |
| |  | Medtronic 3391 |
| **Abbott / St. Jude** |  | Infinity 4-channel lead 6166 & 6168 |
| |  | Infinity 4-channel lead 6167 & 6169 |
| |  | Infinity directional lead 6170 & 6172 |
| |  | Infinity directional lead 6171 & 6173 |

**Table 3.** Currently commercially available electrodes for DBS [36]

Other companies such as PINS Medical, SceneRay and Nexstim offer distinct types of DBS electrodes, however, they have not been contemplated in this project. NeuroPace Inc. and Aleva Neurotherapeutics SA are emerging companies which are innovative in the market for DBS devices. [37]

## 3.2. FUTURE MARKET PROSPECTIVE

Over all these past years, life expectancy has exponentially increased, as better medical care and better living conditions have played a fundamental role. Additionally, life expectancy has suffered an important growth due to the decrease of infant mortality across the world. As people reach an older age, the prevalence of neurodegenerative diseases has increased considerably together with surgical procedures for PD, and since society has become aware of neurological diseases and their long-term treatments, such as deep brain stimulation, *Gran View Research Inc.* estimates that the market size by product of DBS will be raised in the forecast period. [37] A further element that plays a major role in the market is the constant technological advancement, such as robot-assisted implantation, improving microelectrode design, rechargeable IPGs, within others mentioned on section 2.2. beforehand.

The insight of the future of DBS comprises a less invasive, safer and more personalised and effective technique; eliminating the anterior-wall chest IPG and extension cables, increasing the battery life of the smaller cranialised IPG, together with electrodes able of sensing and stimulating. The improvement of sophisticated imaging techniques such as > 3 Teslas (T) MRI systems will enhance the identification of brain structures and to validate the possible physiological effects of the electric current in the brain target. [18] Nevertheless, being such an emerging technology, it is important to consider the ethical, security and privacy effects that this methodology and the respective technological advances entail.

# 4. LEGISLATION AND REGULATION

This project is based on an accuracy assessment of lead placement in stereotactic surgery regarding PD. As it has been fully developed in Barcelona, Spain, the legal requirements taken in to account follow the Spanish legislation.

Firstly, as the studio is based on real data from patients which were acquired in the Hospital Clínic of Barcelona, the information has to be preserved by the *Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales.* As it can be seen in *Disposición adicional decimoséptima* [38] focused on health data treatment, the study will be allowed if the data used are for biomedical research purposes and if all of them have been previously anonymised without being able to obtain personal information about the patient from them.

Deep brain stimulation, in this particular project, consists of the introduction of two electrodes in the subthalamic nucleus and a subcutaneous neurostimulator in the anterior chest wall. Hence, these devices must fulfil the European Commission legislation, specifically the directive of Council Directive 90/385/EEC regarding Active Implantable Medical Devices. According to the European Commission, an active medical device is defined as "*any medical device relying for its functioning on a source of electrical energy or any source of power other than that directly generated by the human body or gravity*" whilst an active implantable medical device, "*any active medical device which is intended to be totally or partially introduced, surgically or medically, into the human body or by medical intervention into a natural orifice, and which is intended to remain after the procedure*". [39] As a result, design and construction of the electrodes and the pulse generation will have to follow the detailed requirements, alongside being identified with the CE mark.

Nonetheless, the 26th of May of 2021 a new European Union directive has been implemented on the clinical investigation and sale of medical devices for human use, the Regulation (EU) 2017/745. It came into force the 25th of May of 2017, and it concerns both medical devices and active implantable devices. [40]

# 5. CONCEPTION ENGINEERING

All the solutions studied in order to compute the vector assessment have been comprised in Table 4. The study of solutions describes into further detail all the approaches which could be proposed to accomplish the objectives set for this study.

| | SOLUTIONS STUDIED |
|---|---|
| **Data Acquisition and Preprocessing** | • Stealth Station S8 Medtronic Inc.<br>• Lead DBS Matlab<br>• BRAINLAB Elements |
| **Programming Environment** | • Matlab<br>• RStudio<br>• Python |

**Table 4.** Study of solutions for the fulfilment of the study

## 5.1. STUDY OF SOLUTIONS

### 5.1.1. DATA ACQUISITION AND PREPROCESSING

In order to obtain and compute the preprocessing of the patient's data, including the coregister of a preoperative MRI and a postoperative CT and the further coordinate acquisition for the accuracy assessment, three different programs have been studied.

**StealthStation S8** is a software application developed by Medtronic Inc. designed to facilitate the neurosurgical navigation and the planning of interventions, both cranial and spinal. It is a software which displays a high number of applications and characteristics, as it presents automatic 3-D segmentation tools, anatomical and structural visualisations, surgical planning approach with virtual craniotomy and virtual endoscope tools and image merging from a wide range of imaging systems.

The main advantage of StealthStation S8 is that it is a very graphical and intuitive interface to use, facilitating understanding. On the other hand, obtaining the coordinates is a very simple process once the commissures are determined and the brain is divided into the two hemispheres. It also has the option of viewing the atlas superimposed to check the anatomical region where the electrodes are located. Conversely, as being a Medtronic program that is associated with all the machinery used for navigation in the operating room, it is a very costly and expensive software, which is only available at the Hospital Clínic or in those clinics that have an agreement with the company. [41]

Figure 14 displays the main screen of the software with the reference electrodes obtained from the atlas, and the placed during surgery. On the right, the coordinates are shown.

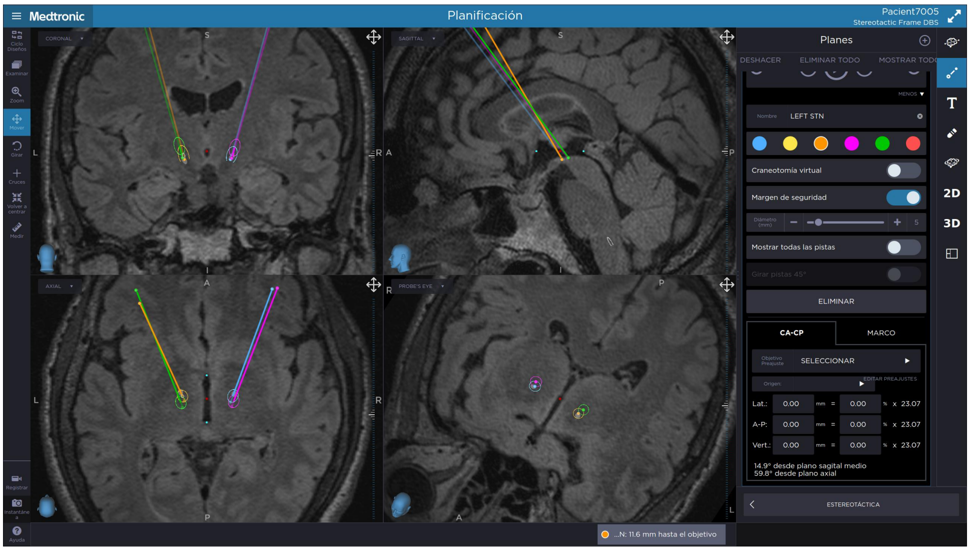


**Figure 14.** StealthStation S8 Medtronic main screen

**Lead DBS Matlab** is a free Matlab toolbox focused on DBS electrode reconstructions and computer simulations based on postoperative MRI and CT imaging. Lead DBS allows the user to locate and visualise in a 3D environment DBS electrodes, taking into account a high number of subcortical atlases and whole-brain parcellations ceded by several authors. In addition, both functional and structural whole-brain connectome analyses could also be computed.

The program is not as intuitive as the mentioned beforehand, and one must have a notion of programming and neuroimaging to understand and use it correctly. Nevertheless, the process of three-dimensional modelling of the electrodes was not automated and depended on the author and this can lead to a large margin of error. On the other hand, DBS electrode simulations could be performed but the relevant coordinates were not obtained. [42] The visualisation of the three dimensional modelling accomplished by the toolbox is shown in Figure 15.

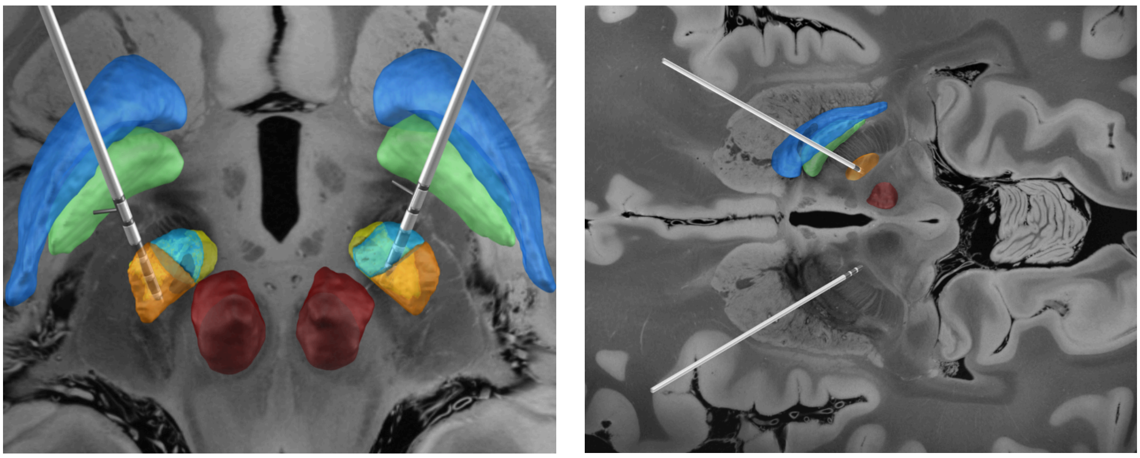

**Figure 15.** Lead DBS Matlab 3-D modelling of electrodes [42]

**BRAINLAB Elements** is a software program designed by Brainlab which includes multiple clinical specialties, such as interactive and automatic segmentation applications regarding image guided surgical planning. DBS electrode placement as well as stereotactic planning can be computed (Figure 16), and all the coordinates and data needed for this study are achievable. Nonetheless, it is also a very expensive program and it has compatibility only with the electrode models developed by Boston Scientific, thus in the Hospital Clínic of Barcelona stereotactic surgeries are performed using Medtronic electrodes. [43] [44]

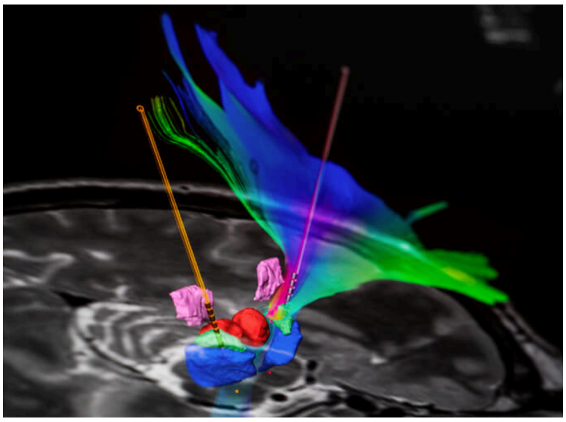

**Figure 16.** Brainlab Elements Stereotaxy planning [44]

### 5.1.2. PROGRAMMING ENVIRONMENT

In order to accomplish the accuracy assessment including the statistical analysis, different softwares can be used: MATLAB, RStudio and Python. Each of them are detailed below.

**MATLAB** is designed presenting different toolboxes for data analysis, image processing, visualisation, within much others. It is a computing environment which facilitates iterative analysis as well as design processes, and it expresses the mathematics of matrices and arrays directly. [45] Nonetheless, for its use an annual license of a very high cost is required, and this is given by the University of Barcelona itself.

**RStudio** uses the programming environment of R, which is specially focused on statistical analysis and graphical representation of them in a data science environment. RStudio is a free and open source software and includes a big number of R packages for data science, Machine Intelligence, interoperability between Python and R, and much others. [46]

**Python** is a programming software characterised by its efficiency, general-purpose and flexible environment. It is one of the most popular programming languages and it also includes packages such as *NumPy*, *Matplotlib* or *SciPy*. It is an open source software which makes the program accessible to every individual.

## 5.2. PROPOSED SOLUTIONS

Once all the solutions have been thoroughly studied comparing all their characteristics and applying them to the objectives of this study, the following solutions have been selected.

The programming environment selected has been MATLAB, as it presents a facility with mathematical expressions as well as in the relevant statistical study and graphical representations. As it is only necessary to calculate the relevant values as well as represent them, it does not require external persons to have the license, as the author has it.

Moreover, data acquisition as well as pre processing and obtaining all the coordinates necessary to fulfil the accuracy assessment were obtained using StealthStation S8, the Medtronic cranial and spinal surgical planning software available at the Hospital Clínic of Barcelona. Considering that it is a very intuitive and very graphical program, it makes the process of obtaining the necessary data quick and simple.

Originally the author wanted to use Lead DBS Matlab, whereas it is a free open source program accessible for anyone who wishes to access it, alongside being a toolbox of MATLAB, hence it requires the license of MATLAB. Nonetheless, finally it was not chosen as it does not present the coordinates in a precise way, due to the dependency of a lot of knowledge of brain's anatomy of the author, and left a fairly large margin of error.

Lastly, the BRAINLAB Elements program could have been used, however, since the electrodes implanted at the Hospital Clínic of Barcelona correspond to the Medtronic company, it was considered that the study would be more accurate if the preprocessing was also carried out with the company's software.

# 6. DETAIL ENGINEERING

As it has been mentioned beforehand, this study consists of the co-registration of preoperative MRI images and postoperative CT images and data acquisition to obtain the x, y and z coordinates (AC-PC coordinates) of the electrode located specifically in the STN, which have been acquired for both hemispheres.

The methodology followed has used a population of 76 patients with Parkinson's disease who have undergone a STN-DBS at the Hospital Clínic of Barcelona from 2015 to 2020, whose brain electrodes have been implanted with verification of intraoperative imaging, under general anaesthesia.

Secondly, by terms of using MATLAB and the coordinates, the vector error is calculated and an accuracy assessment is computed. The results are graphically represented in two scatter plots and the regression line, as well as the equation, are found.

Finally, the results are divided into the statistical analysis, consisting of the mean, the standard deviation and a Student T-test. To conclude, a clinical appraisal is analysed, using each patient's medical histories once they have been previously anonymised.

## 6.1. DATA

Referring back to the population used for the study, the preoperative MRI images as well as postoperative CT images once the STN-DBS was accomplished has been utilised of 76 patients in the temporal space of 2015 to 2020. All the data was previously anonymised to ensure that no relationship could be established between the images and the clinical information used of the patient with his name or other personal data. Likewise, medical histories have been used.

Therefore, the historical cohort of conscious operated patients under local anaesthesia has been excluded in this project, in which the intervention performed entailed a series of electro-physiological and clinical tests to verify the correct positioning of the electrodes. This was essential during the period 1994-2014, in which the stereotactic intraoperative image integrated with the neuronavigation systems was not available.

The benefits of operating on the patient under general anaesthesia are important and remarkable, both for the patient undergoing the intervention as well as for the healthcare system of the country. Some of these benefits are precised on Table 5.

| Benefits of a STN-DBS surgical procedure carried under general anaesthesia |
|---|
| Prevents the patient's suffering |
| Eliminate the need to withdraw all medication in order to assess symptomatology |
| Eliminate the need to introduce electro-physiological recording microelectrodes, which are more dangerous as they present a sharper structure |
| Reduces duration of the intervention, which is directly related to the risk of infection, within others. |
| Shortens hospital admission time |

**Table 5.** Benefits of the surgical intervention of STN-DBS under general anaesthesia

## 6.2. CO-REGISTRATION AND COORDINATES ACQUIREMENT

Co-registration techniques have been fulfilled using StealthStation S8 designed by Medtronic Inc, which is available at the Hospital Clínic of Barcelona. The desired images of each patient are selected and co-registered automatically by intrinsic algorithms of the software.

The company program is intuitive and its main menu is shown in Figure 17. It is composed of 8 characteristics which are specifically detailed in Table 6: CA-CP, Plans, Annotations, Plan overlap, Atlas, 2D views, 3D view and designs. In this study, the most used were CA-CP to obtain both commissures, Plans to acquire target points and the entry points coordinates and 2D views to control the coregister between CT and MRI.


**Figure 17.** Menu available at StealthStation S8 in "Stereotactic DBS Frame"

| | **StealthStation S8 Characteristics** |
|---|---|
| **CA - CP** | Used in order to define the AP and the PC, as well as the intermediate line and the AC-PC distance |
| **Plans** | Fundamental tool to implement the planning of the intervention, obtaining the theoretical coordinates as well as the real ones |
| **Annotations** | To mark a point of anatomy or pathology, and they can be placed at the point of navigation in order to mark a location |
| **Plan Overlap** | Allows you to merge different created plans |
| **Atlas** | A fully integrated Schaltenbrand Wahren Atlas and a Talairach grid which grant interaction and facilitates obtaining a better understanding of the brain's anatomy |
| **2D views** | Two-dimensional viewing of the selected images (CT and MRI) and its coregistration, together with having the ability of changing some of its imaging properties |
| **3D views** | Three-dimensional model obtained based on the images |
| **Designs** | You can adapt the interface and choose the preview, how many screens, if you want them to be axial planes, within others. It even permits the design of an interface which is more comfortable |

**Table 6.** Software characteristics and its main function

Furthermore, once the co-registration is verified by the system and by the author, the establishment of the anterior commissure (AC) along with the posterior commissure (PC) must be performed to obtain the desired AC-PC coordinates. Three images are imported into the software: a postoperative CT, a T1 section of MRI and FLAIR T2 MRI.

This process consists of the location by the author of each structure, leading to a small margin of error, as the coordinates refer to the AC-PC line in the axial plane. The AC-PC line is the line connecting the anterior and posterior commissure, separating the brain into two equal parts; in two different hemispheres. The origin of the AC-PC line comes from the ventriculography. The AC-PC line can be certainly observed in Figure 18.

Thereupon, firstly both commissures are detected and once they are finally selected and the intermediate plane is also determined, the software calculates the AC-PC distance. To detect the location of the commissures, it is only required to use the T2 FLAIR image of the patient's MRI, as this is where the clearest and most accurate anatomical structure is shown.

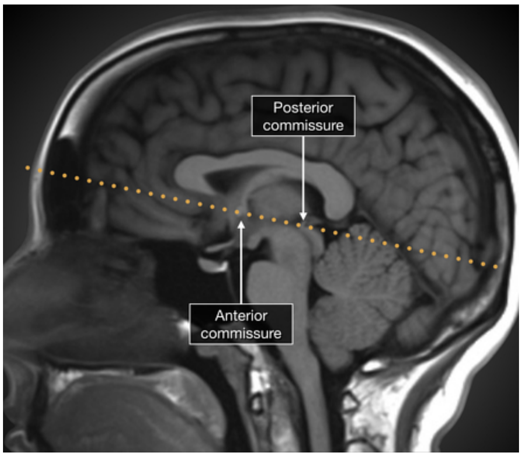


**Figure 18.** AC-PC line seen in an axial MRI image [47]

Once the stated process is achieved, the methodology proceeds to the detection of the DBS electrodes. For this case, the T1 co-registered with the CT scan is used, so the anatomical structures with the electrodes superimposed on them are witnessed. It is worth emphasising that an image from a CT scan presents many artefacts, especially in terms of metal objects such as the electrodes. That is why it will be necessary to raise the level of the image to obtain the most faithful electrode possible to reality, with a diameter of 1.27mm with regard to the model used, the Medtronic 3389. Once this procedure has been finalised, the coordinates of the electrodes will be obtained in the "Plans" section, concerning the Schaltenbrand AC-PC line.

In neurofunctional interventions, the brain coordinates used are named the **AC-PC coordinates**. Figure 19 shows the coordinates with respect to the commissures and the target, where a localiser box is placed on the frame and it generates a coordinate system calculated in reference of the AC-PC line. This system corresponds to the *Talairach* atlas, and assuming that the brain retains the individual shape and size. [48] [49] As aforementioned, the landmarks are the AC and the PC, and the coordinate axes are defined according to these characteristics:

- The origin of the coordinate system is in the AC.
- <u>X-axis (lateral)</u>: It goes towards the right side of the brain.
- <u>Y-axis (antero-posterior)</u>: It goes towards the front of the brain.
- <u>Z-axis (vertical)</u>: It goes towards the top of the brain.

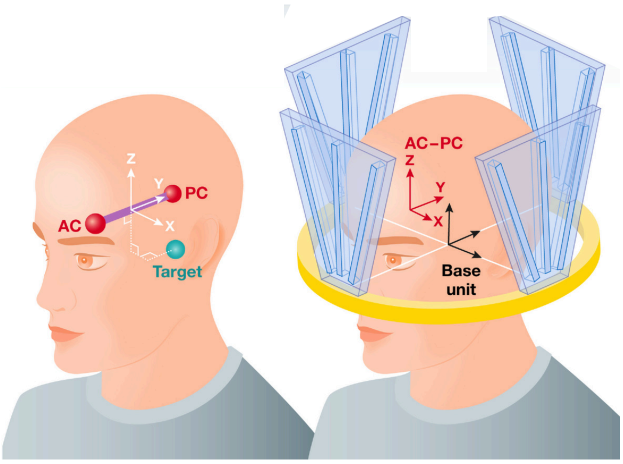


**Figure 19.** AC-PC coordinates and base unit [48]

In general conditions, the atlas states that the coordinated in the right hemisphere for the STN are located in the x (lateral), y (antero-posterior) and z (superior) of 12mm, -4mm and -4mm, whereas in the left hemisphere the coordinates x, y and z respectively are of -12mm, -4mm and -4mm.

The software has a built-in atlas, a Schaltenbrand-Wahren Atlas alongside a Talairach grid, and therefore once the location of the electrode has been selected following the co-registration of the images, the theoretical electrode of the atlas can be superimposed and the difference can be seen visually. The software also has the option to overlay the atlas and validate the anatomical region where the electrodes are located.

The Schaltenbrand-Wahren Atlas, in blue colour, overlaid onto the coregistered image is exhibited in Figure 20. The brain image observed corresponds to a T2 FLAIR MRI, and the small grey artefacts shown correspond to the CT image, specifically to the DBS electrodes. The use of the Schaltenbrand-Wahren Atlas allows the visual and easy anatomical location of the electrodes as well as of brain structures. In this specific case, it serves to verify that the electrodes have been correctly implanted in the STN, the desired target.

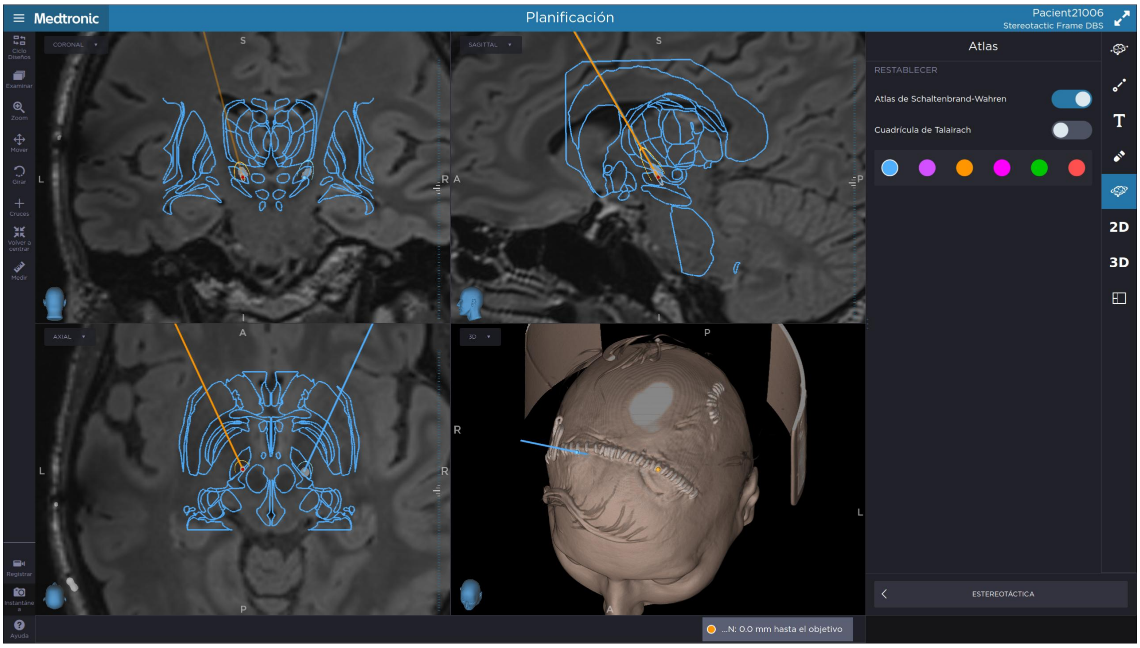


**Figure 20.** Schaltenbrand-Wahren Atlas overlaid with the coregistered image of MRI T2 and CT

Additionally, Figure 21 comprises the co-registration of T1 MRI and CT scan and the location of the real electrodes and the theoretical electrodes. The images are seen in coronal (top left), sagittal (top right), axial (bottom left) and probe's eye (bottom right). The blue and the orange electrodes correspond to the real implanted electrodes during the intervention, for the right and the left hemisphere respectively. Contrariwise, the pink and green electrodes refer to the theoretical electrodes following the atlas' coordinates.

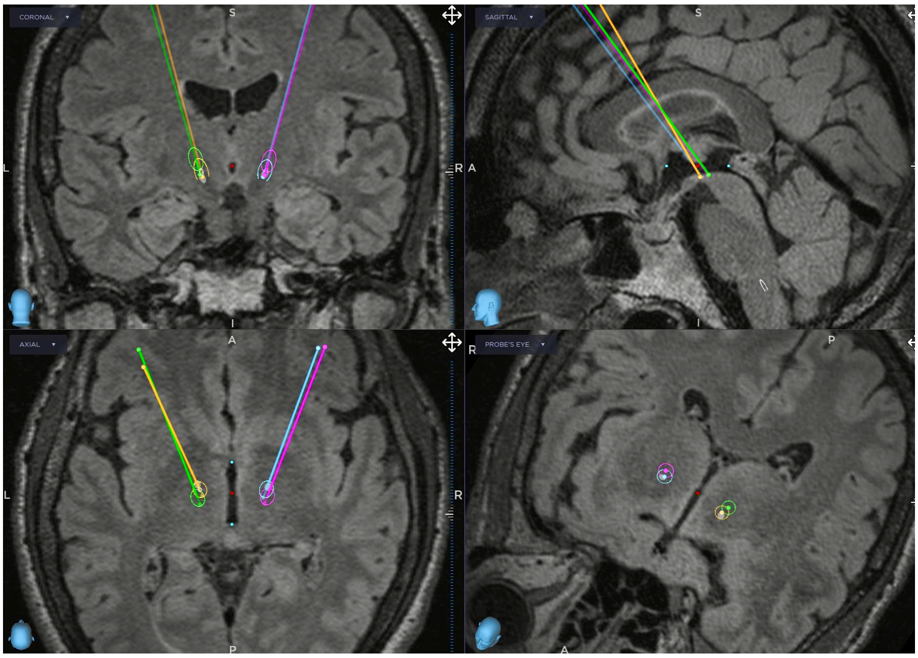

**Figure 21.** Representation of the real (blue and orange) and the theoretical (pink and green) electrodes

Following the same procedure mentioned, the coordinates of the entry points can be found, since the CT image is composed of many slices, it can be observed exactly from which point in the brain the electrode enters from the stereotactic framework. Thus, the software will not only place the electrode on the required target, the STN, as it locates the correct entry point, hence marking the actual trajectory.

To achieve the deviation error, it is necessary to use the plans made by the neurosurgeons prior to the intervention, merge them, and calculate the differences. This process was intended to be followed for the entire study population but was not possible as the available data was erased before the study was computed.

All the methodology is accomplished with each patient and all the data, both entry points and target points, are saved in a file. Lastly, each patient will have twelve coordinate values. Six will correspond to the entry points, which have finally not been used in this study, and the other six to the target points, likewise for the respective brain hemisphere.

## 6.3. ACCURACY ASSESSMENT

To accomplish a validation of the current surgical technique, an accuracy assessment to assess electrode placement has been fulfilled using MATLAB (see Annex) by terms of calculating the vector error to obtain the targeting accuracy in all the data acquired. [50] As mentioned earlier, the deviation off trajectory was intended to be studied, however, the available data was erased.

I. The **vector error** is the distance between the position of the centre of the target DBS electrode contact and the desired target location which is determined by the euclidean distance between these two specific points. The vector error corresponds to the true accuracy.

II. The **deviation off the trajectory** describes the perpendicular distance from the target electrode to the planned trajectory only in the axial plane, hence the deviation in the radial plan. The off-trajectory error are more complex for them to be corrected.

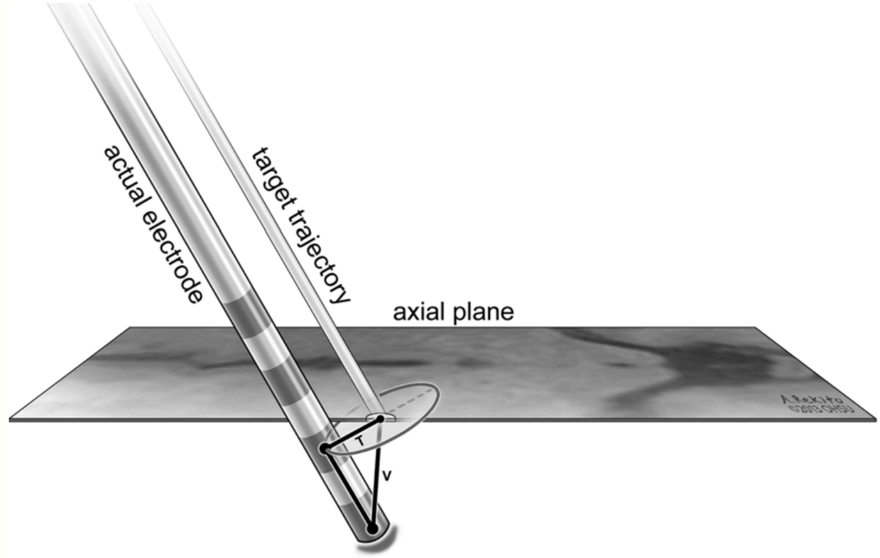


**Figure 22.** Vector error (v) and Trajectory error (T) representation [50]

Figure 22 displays a graphical representation in order to obtain a better understanding of the vector error and the off-deviation error considering the actual electrode implanted in the intervention and the target trajectory, as well as the target coordinates obtained from the plan and the atlas. Moreover, Figure 23 exhibits the different definitions of TE, in this case, established the VE as d (Euclidean error) and r the trajectory error.

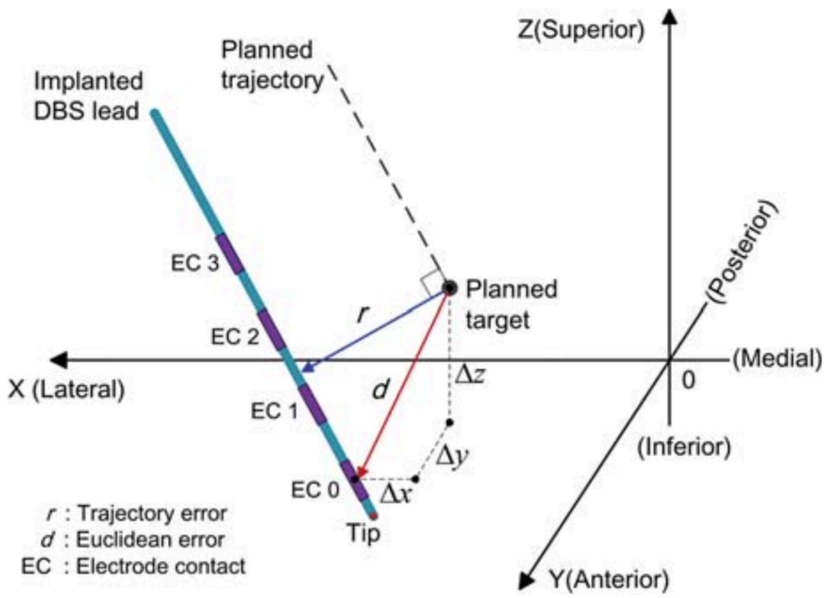


**Figure 23.** Graphical representation of different definitions of TE [17]

### 6.3.1. VECTOR ERROR

The vector error (VE) calculation, computed with MATLAB with the code being available at the Annex, requires knowledge of the real x, y and z coordinates and also of the theoretical coordinates obtained through the atlas. The atlas's coordinates corresponding to the STN for both hemispheres, as previously stated, are outlined in Table 7.

| SCHALTENBRAND-WAHREN ATLAS'S COORDINATES STN | |
|---|---|
| **Right Hemisphere** | **Left Hemisphere** |
| • X: 12.00 mm<br>• Y: -4.00 mm<br>• Z: -4.00 mm | • X: -12.00 mm<br>• Y: -4.00 mm<br>• Z: -4.00mm |

**Table 7.** Theoretical coordinates of the STN in both hemispheres

Once knowing the theoretical coordinates, the author proceeded to the acquisition of real data with the methodology mentioned in the section above. To calculate the VE, performed for each patient twice, once for each hemisphere, the data were applied and the value was calculated by terms of using Equation 1.

$$VE = \sqrt{(x_1 - x_0)^2 + (y_1 - y_0)^2 + (z_1 - z_0)^2} \tag{1}$$

The VE calculation has been computed using the programming environment MATLAB specified in section 5.1. by establishing an iterative loop to perform the accuracy estimation. The data were stored in a 76-row, 7-column *CSV* file, where the rows correspond to the patients and the first column to the patient's set number and the other six to the respective target point coordinates for each cerebral hemisphere.

The final result obtained once the equation has been calculated has been saved in a *CSV* file with two columns and 76 rows, one column corresponding to the accuracy of the right hemisphere and the other to the accuracy of the hemisphere left one.

## 6.4. STATISTICAL ANALYSIS

Besides the accuracy assessment, a paired Student t-test has been computed in order to provide a hypothesis test of the population's means difference for a pair of samples, which in this case are the vector accuracy of the right hemisphere and the vector accuracy of the left hemisphere.

Furthermore, both the mean and the standard deviation of each VE has been accomplished. Additionally, the absolute averages of each coordinate, regardless of accuracy, have also been calculated.

## 6.5. RESULTS

### 6.5.1. TARGETING ACCURACY

The targeting accuracy has been assessed for 76 patients which all have undergone the same intervention with the same image guided and image verified technique. Once the results were analysed, a study of outliers with above-average values was made and two patients who had the target to a brain structure other than STN were discarded, as the electrode had been implanted in the VIM and they were not patients with Parkinson's disease, as they had essential tremor. These two patients have been rejected and the relevant graphical representations have been made again with the 74 patients who do have the electrodes implanted in the STN and therefore have PD. All the coordinates for each patient are specified at the Annex.

Referring to the right hemisphere, the computed mean of the vector error is of 1.923 mm and it's SD is of 1.107. Further to this, the absolute average of the x axis is of 11.482 mm, the y axis of -2.673 mm and the z axis of -3.824 mm. These results regarding are detailed in Table 8.

| COORDINATES RESULT (RIGHT HEMISPHERE) | | | |
|---|---|---|---|
| **COORDINATES** | **Atlas** (mm) | **Real Average** (mm) | **Error Percentage** (%) |
| **X** | 12 | 11.482 | 4.32% |
| **Y** | -4 | -2.673 | 33.18% |
| **Z** | -4 | -3.824 | 4.40% |

**Table 8.** Results regarding coordinates for the right hemisphere, n = 74

The results in Table 8 show that the mean is quite close to the value theoretically obtained by the atlas. Thus, the coordinate axis that presents a greater difference in this case would be the Y axis, with a difference in absolute value of 1.327 mm. Thus, the largest error rate is that of the Y axis representing 33.18% error. Nonetheless, both the x and z axis have a lower error percentage which is estimated to be around 4%.

Moreover, regarding the left hemisphere, the computed mean of the targeting accuracy is of 2.364 mm, resulting in a value 18% higher and greater than the average accuracy in the right hemisphere. On the other hand, the SD for the left hemisphere has a value of 1.065. Regarding the real coordinates and it's absolute average, the x axis average is of -10.753 mm, whilst the y axis -2.629 mm and the z axis -3.840. The coordinate results of the left hemisphere are specified in Table 9.

| COORDINATES RESULT (LEFT HEMISPHERE) | | | |
|---|---|---|---|
| **COORDINATES** | **Atlas** (mm) | **Real Average** (mm) | **Error Percentage** (%) |
| **X** | -12 | -10.753 | 10.39% |
| **Y** | -4 | -2.629 | 34.28% |
| **Z** | -4 | -3.840 | 4.00% |

**Table 9.** Results regarding coordinates for the left hemisphere, n = 74

The coordinate axis that presents a greater difference with respect to the theoretical value is, again, the Y axis. Nevertheless, in the left hemisphere the X axis presents a more remarkable difference in comparison with the right hemisphere.

It is observed that, in terms of coordinate positions, there is a greater difference between theoretical and real values in the left hemisphere than in the right hemisphere. Furthermore, Table 10 shows the results obtained from the mean and standard deviation in both hemispheres.

| ACCURACY RESULTS | | | |
|---|---|---|---|
| RIGHT | | LEFT | |
| **Mean** (mm) | **Standard Deviation** | **Mean** (mm) | **Standard Deviation** |
| 1.923 | 1.107 | 2.364 | 1.065 |

**Table 10.** Results regarding accuracy for both hemispheres, n = 74

The results shown in Table 10 of the TE specify that in the 74 patients who were reviewed and analysed in this study, the electrodes were implanted more displaced in the left hemisphere, since the averages differ by 0.441 mm. Whether demanding to review the real coordinates and the specific value of the respective TE for each of the 74 patients, see the Annexes section.

The result of the Student t-test gives a **p-value** of $1.384 \cdot 10^{-4}$. Hence, since it is a p-value which is lower than 0.005, it means that this study gives results which are statistically significant.

Once all the calculations have been performed, one graphical representation in scatter plot mode has been computed for the right error vector and another for the left error vector, which are respectively Figures 24 and 25.

In the figures, the x-axis corresponds to the error vector and the y-axis to the distance from the origin (which would be the AC-PC line as discussed above) to the tip of the electrode. This distance is the value of x for each hemisphere.

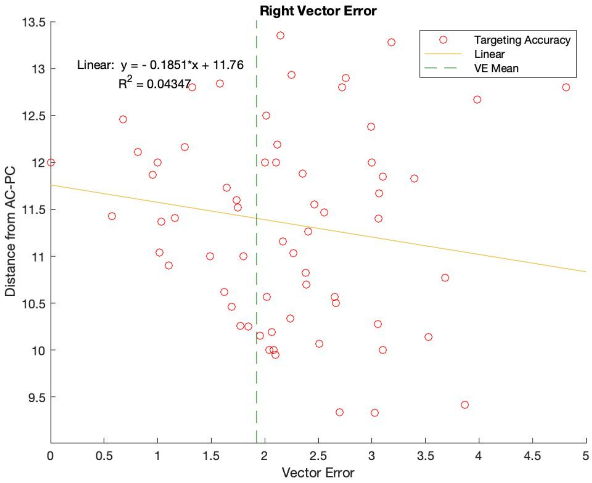


**Figure 24.** VE scatter plot for the right cerebral hemisphere

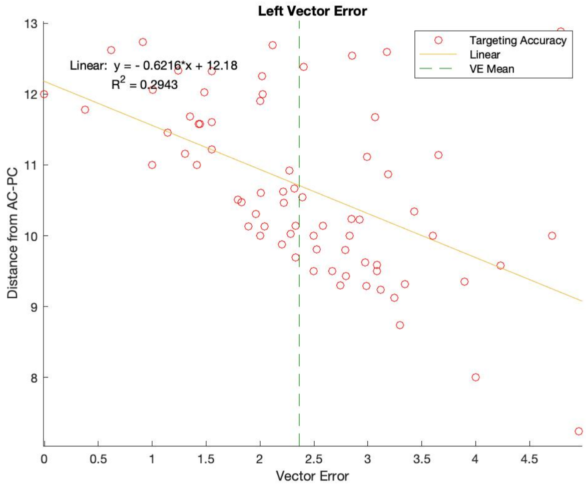


**Figure 25.** VE scatter plot for the left cerebral hemisphere

Both scatter plots show a similar relationship between the vector error and the distance from AC-PC, which directly depends on the cerebral anatomy of each patient. It can be seen that they follow a similar trajectory, although it is true that in both cases there are certain outliers. These outliers may be due to poor identification of the AC-PC line while coordinates were being acquired, as it was a subjective process and, if done incorrectly, this was hampered in terms of error.

In the left hemisphere, the cases are spread out but it is estimated that most are between 1.5mm and 3.5mm error vector, while in the right hemisphere the data are scattered more evenly across the graph covering almost all values. However, the range of the error that comprises most of the samples is between 1mm and 3mm, which reflects that this TE is slightly smaller in the right hemisphere than in the left.

### 6.5.2. CLINICAL APPRAISAL

To perform a study of the clinic and the symptoms before and after the intervention, the process was performed by setting a threshold of 3 mm, meaning any patient who in one of the hemispheres had a VE equal to or greater than 3 mm was included in the study of symptomatology. By following this methodology two outliers patients were discarded, where one had approximately TE at 6mm, for being patients with essential tremor and having a different target to STN, as it was VIM. Hence, the methodology has comprised 26 patients, two of which were rejected for having the target in another brain structure, ending with 24 patients exceeding the threshold of a VE greater than or equal to 3mm.

In general, all patients experience a fairly sudden improvement before electrode implantation and stimulation and afterwards, thus notoriously reducing their motor symptoms which may include bradykinesia and tremors. Therefore, DBS surgery improves the quality of life of patients because, for example, patients who previously could not walk due to the disease could now do so more easily.

However, it is true that the surgery outcomes depend mostly on the adaptation of each patient, and nearly all of them will have to continue with treatment, such as levodopa, for life. Nevertheless, there have also been cases where the medication has been withdrawn and the patient presents satisfaction and enhancement regarding motor symptomatology.

As mentioned in the prior "Background" section, the approach to record a longitudinal progression of the disease is to follow the UPDRS scale, focusing specifically on Part 3 which copes with patient motor assessment.

In general, a large majority of patients show a good evolution once the electrodes are implanted with a reduction in the motor symptoms of PD. Notwithstanding, patients typically continue to present dyskinesias, which normally appears after years of medical treatment with levodopa, and gait freezing, which are short episodes of an inability to move the feet although having the intention to walk.

The most exemplary and enlightening clinical results are as follows:

- Patient 57 presented an error of almost 5mm, concerning the atlas, in an electrode, and was treated because they had a problem with the stereotactic frame during the intervention and had to reoperate to reposition the electrode correctly. Once the methodology was followed correctly, the patient improved remarkably.
- With an error of 3.2mm, Patient 87 suffered a bilateral capsular effect and the operation had to be repeated to place the electrode in a medial position.
- Explantation of all the DBS system was accomplished to Patient 21, due to the lack of effectiveness presenting an error of 3.2mm in the left hemisphere. Additionally, the device presented MRI artefacts that would prevent a correct delimitation of the surgical target. A new system was implanted and the patient halted taking any anti-Parkinson’s medication, displaying very favourable results with only a little gait freezing.
- Patient 42 presented an error of 3 in both hemispheres and firstly there was a neurostimulatory infection, specifically a serosanguinuous exudate through a surgical wound. Thus, another operation was performed which consisted of removing the entire implanted system and relocating the entire system. The patient, once the revision surgery was done, appeared to have a few dyskinesias and a freezing gait.

# 7. DISCUSSION AND FUTURE RESEARCH

## 7.1. DISCUSSION

The intervention of STN-DBS as a treatment for Parkinson's gives very favourable results for the patient, thus decreasing a large majority of their motor symptoms. However, normally the patient once undergoing the intervention must continue treatment for PD such as levodopa as not all motor symptoms disappear, as well as it could get worse over the years.

In Figure 26 molecular mechanisms initiated or deactivated by stimulation on basal ganglia networks are detailed. It can be observed that in the case of Parkinson's disease, the inhibitory pathways of both the neurons at the substantia nigra pars reticulata (SNr) and substantia nigra pars compacta (SNc) are increased, as well as the excitatory pathways of STN. This is because the STN receives fewer inhibitory signals from the external globus pallidus (GPe) and hence sends greater excitatory signals to the GPi and the SNr. Therefore, there is mostly an increase in the pathways, causing decompensation and imbalance.

In addition, there is a loss of dopaminergic neurons from the SNc to the putamen. On account of the incorporation of stimulation with the DBS electrode, some effects that were increased previously will result having a decreased behaviour, including the excitatory pathway of the STN to the SNr and GPi. Whereas the STN is compensated, the stimuli that will reach the thalamus from the GPi and SNr will be balanced and return to their normal behaviour. Anyhow, a significant loss of dopaminergic neurons will persist after STN-DBS intervention as seen on 26.c. Stimulation serves to balance the STN and therefore compensate for the other excitatory or inhibitory pathways.

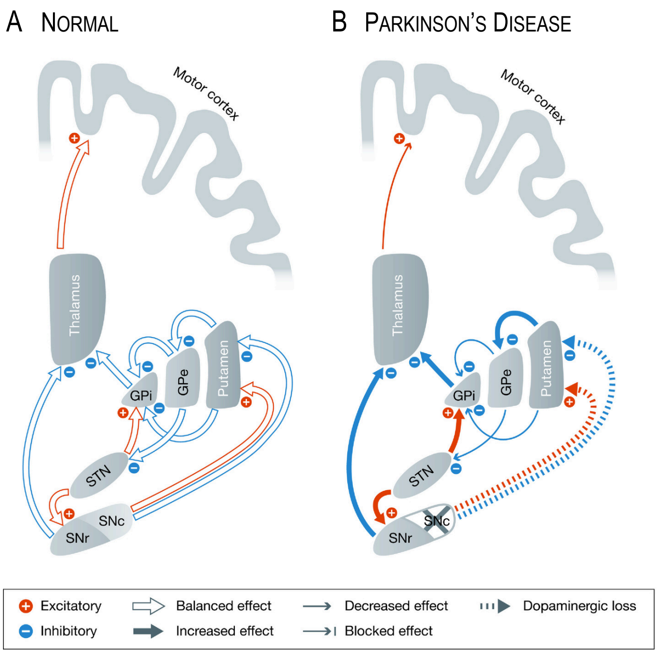


**Figure 26.** Molecular mechanisms of basal ganglia networks in **(A)** Normal brain **(B)** PD brain **(C)** STN-DBS brain after stimulation [48]

Thus, during this study, it has been possible to verify that the realisation of the STN-DBS intervention through the image-guided and image-verified technique by means of intraoperative CT with the O-Arm, used in the Hospital Clínic, very positive clinical results are obtained where the reduction of motor symptoms are evidenced. The average TE was 1.923 mm ± 1.107 on the right hemisphere and 2.364 mm ± 1.065 on the left hemisphere. However, it is important to point out that this technique is not performed in many hospitals in Catalonia, yet almost all centres use the **microelectrode recording** (MER) methodology, used to identify brain structures during the intervention as it permits the recording of electrical activity, and each brain structure has a unique pattern of it. The principal problem with this technique is that the patient has to discontinue the use of all medications prior to the surgery, since it is necessary for the surgeon to observe the electrical patterns of the brain structures presenting the disease, and the medication could create false negatives and hide a possible difference in pattern.

MER-guided surgery is also a precise technique and has good results [51], but contrarily it has setbacks that are mainly the withdrawal of medication before surgery, as well as the process is much longer as performing the electrical registration is dense. On the other hand, the patient is usually required to be awake, likewise causing anxiety. These three disadvantages of MER are eliminated using the image-guided technique, as the patient may be subjected to the necessary medication and also slept under general anaesthesia as the target on the STN is well defined and the patient does not need to remain awake.

This study has fulfilled the primary objective of validating the technique used in the Hospital Clínic using intraoperative CT and prior planning. Hereby, the importance of accuracy and precision in this type of intervention is evidenced, and it is a field where technological advances are very present and are constantly evolving to try to achieve an error as close to zero as possible.

Still, despite using this technique at the Hospital Clínic and achieving significant results, there have been a couple of cases where electrodes were incorrectly implanted with a visible error, and the only solution to make the electrodes perform their function is to reoperate the patient. The technique is used with the stereotactic framework, and with the boom we are experiencing in robotics, a robotic arm connected directly to the neuronavigation system could be implemented in the operating room which would obtain the coordinates in real-time and compare them with those defined during the planning. It would be a very important advance to use a robotic arm that would detect at the time where it is and connect it to the virtual map, thus establishing a correlation between the real body and the virtual body.

Lastly, it is important to emphasise that possible errors may have occurred during the whole course of the study. Mostly, errors can appear from the establishment of the two commissures during image processing with Medtronic software. The author does not have the same knowledge of brain anatomy as a neurosurgery specialist, which is usually responsible of performing this process, and if these commissures are incorrectly established, being the point of origin of the coordinates, they could be affected and could change the results. Still, the results are generally satisfactory as they present a correlation with the clinic symptomatology of the patient. Other errors such as the acquisition of coordinates from patients who did not have PD and had essential tremor, thus establishing the point of stimulation in a structure other than STN, have been reversible errors as they have been removed from the base of patients.

## 7.2. FUTURE RESEARCH

Considering that this study has focused on the technique currently practiced using stereotactic framework and intraoperative CT, this allows for much margin of improvement due to the evolution that medical technology is currently undergoing. Different advances in biomedical engineering can be applied to obtain more accurate results, such as the use of robotics integrated into surgery or artificial intelligence. As mentioned beforehand, the insertion of a robotic arm in the operating room that is fully integrated with the intraoperative CT as well as with the neuronavigation would eliminate possible human errors when fulfilling the burr hole and also possible errors due to the incorrect placement or other problems with the stereotactic framework. On the other hand, it would be important to implement an artificial intelligence technique that would detect the error of the trajectory as well as the error of the target in real-time. This advance could be carried out by placing a positional sensor at the tip of the inserted electrode and connecting it directly with the navigation or with some other system in the operating room with the aim that it represents the numerical value of the error in real-time, and thus to be able to guide to the surgeon during the whole placement.

Finally, it is significant to acknowledge that during this study the author wanted to perform other calculations such as the error of the trajectory and the error of the entry point of the electrode which were considerable for the validation of the procedure. Neither could be performed as it was necessary to have surgery planning computed by the neurosurgeon and all had been erased from the system. Consequently, as future work to substantiate this technique in an entire approach, these two methodologies could be followed and analysed.

In view of the technological advances that will appear in the near future, it is necessary to highlight the role of biomedical engineers in order to be able to implement it and think about connecting technology with medicine. Thus, biomedical engineering play a very important role in the technological evolution within medical and surgical specialties, focusing on improving the accuracy and utility of techniques, as well as achieving a procedure where the patient is as comfortable as possible.

# 8. TECHNICAL VIABILITY

The technical feasibility corresponds to a SWOT analysis, studying and detailing both external (opportunities and threats) and internal (strengths and weaknesses) factors affecting the project and displayed in Table 11.

| STRENGTHS | WEAKNESSES |
|---|---|
| Internal | Internal |
| ○ Data from 2015 to 2020<br>○ Validation of a current technique<br>○ Provide objective arguments of the technique with general anesthesia<br>○ The use of neuronavigation and planning techniques at the hospital<br>○ Automatic coregistration<br>○ 3T MRI Imaging (dedicated protocol) | ○ Limited software availability<br>○ Margin of error at the coordinates acquisition<br>○ Validation of the system with one electrode model<br>○ Retrospective analysis<br>○ Limited correlation with patient clinical outcome |
| **OPPORTUNITIES** | **THREATS** |
| External | External |
| ○ Alternative non-invasive process to fulfil DBS<br>○ 7T MRI imaging<br>○ Improvements in planning and navigation softwares<br>○ Implementation of IA for error detecting in real-time during the intervention<br>○ Establish a correlation with the clinical outcome (UPDRS III) | ○ New technological approaches to perform DBS interventions<br>○ Authorisation granted by doctors and patients |

**Table 11.** Overview of the SWOT analysis

## 8.1. STRENGTHS

Different strengths have been analysed, which are an intrinsic factor of the project and are helpful for such. Primarily, the patients' data that has been used corresponds to a temporal period going from 2015 to 2020, therefore it corresponds to different years, obtaining some heterogeneous data and realised with different neurosurgeons. Additionally, the first objective of the study is to validate the accuracy of the implantation technique guided exclusively by imaging, which is the principal surgical technique for DBS interventions currently at the Hospital Clínic of Barcelona. In this way, objective arguments can be obtained about the image-guided image-verified technique with the fully anaesthetised patient.

Moreover, it is also an important strength to have been able to use the navigation software used in the hospital during the day to day to plan surgeries, as well as that it has a built-in co-registration mechanism, eliminating possible margins of error. On the other hand, in the Hospital Clínic, there is a dedicated and specific protocol for this type of intervention, where 3T MRI images are taken and used during the intervention, allowing to have standardisation and following a very similar methodology for each patient.

## 8.2. WEAKNESSES

Although the study presents a wide number of strengths, it also has important weaknesses to consider. First of all, as the software is the one used in the hospital it has limited availability. Thus, this is because the program is used by neurosurgeons and is not always available, besides it is only in the hospital and the author has to travel there to acquire any data. Moreover, it is a program from a private company, and therefore there is no public license.

A weakness related to a possible error is that the commissures had to be placed subjectively, and as the author does not have very extensive knowledge of the brain anatomy, it may not be in the most correct place and cause deviations in the coordinates acquirement. On the other hand, the validation has been done exclusively considering the Medtronic 3389 model, and this validation could be modified with other models from the same company or others.

Additionally, this project is a retrospective analysis, focused on patients from 2015 to 2020. This study could be modified in subsequent years with components that have not been considered during the five years included in this study. Thus, there is a limited correlation with the patient's clinic that could be improved with the collaboration of a neurologist.

## 8.3. OPPORTUNITIES

There are a variety of opportunities that this study could benefit from, mainly focused on possible improvements to the DBS technique as well as technological incorporations into the procedure. For example, the alternative non-invasive process to fulfil DBS could mean a non-invasive treatment and preferred by the patient. Moreover, improvements in planning and navigation software could ameliorate the TE, together with the introduction of 7T MRI imaging. Besides, future research focused on artificial intelligence for error detecting in real-time during the procedure could appear. As a continuation of this study, a correlation within the surgical outcomes of the implantation could be established with the patient's symptomatology following the UPDRS III scale, addressed to the motor symptoms of the patient.

## 8.4. THREATS

Finally, of the four categories, threats are the least existing as it is a study of a technique that can evolve very positively in the near future. Notwithstanding, the principal threat of this study, and the DBS techniques, is that authorisation is required both from the doctors and the patients. In addition, data protection is very important and therefore the anonymization of all data is mandatory.

On the other hand, with so many technological advances, and with the emergence of new technologies to perform these interventions, this study could be neglected as it has only validated one procedure which follows a specific protocol: the intervention using a stereotactic framework system and the image-guided image-verified technique.

# 9. ECONOMICAL FEASIBILITY

The theoretical costs have been detailed in order to accomplish this study. The economical feasibility has been divided into human resources, software and hardware, as well as some items such as CT and MRI scans.

Within human resources, the salary which has been taken into account of the student is of 20€ / hour, and the total amount of hours needed to complete the project is 340 hours. Hence, the total cost regarding human resources is of 6.800€. Specifically, the work has been divided into three different sections: firstly the **educational stage**, consisting of 50 hours, where the author did a bibliographic research as well as an analysis of the background prior to making the relevant analysis. Consequently, the **developing** stage of the study, which comprises the conduction of the entire study, from data acquisition to statistical study and clinical relationship. This process entails 150 hours. Finally, the **writing and editing stage**, covering 140 hours, divided into the writing and the oral presentation.

In the software category, both StealthStation S8 and MATLAB have been contemplated. The first software mentioned, as it corresponds to Medtronic, hence a private company, it presents a really high cost. Nonetheless, for this project, the software has been provided by the Hospital Clínic of Barcelona. On the other hand, MATLAB requires an annual license, and in this case is provided by the University of Barcelona to all the students, as the author is.

Finally, StealthStation S8 as well as the private computer, a MacBook Air Apple, are included in the Hardware division. As mentioned beforehand, StealthStation S8, both Software and Hardware, are provided by the Hospital Clínic of Barcelona, thus reducing all the potential cost of it. Moreover, the cost of the computer is estimated to be of 1.300€.

The total cost of the study computed in collaboration with the Hospital Clínic and the University of Barcelona is of 8.100€, and the budget is shown in Table 12.

The cost divided per specific activity is graphically represented in Figure 27, and it can be seen that the higher percentage is for the developmental stage of the project, followed by the writing stage and the private computer. Moreover, Figure 28 displays the cost divided per section, human resources, software and hardware. Most of the cost is clearly visible that it is aimed at human resources, as both the software and part of the hardware has been provided by the collaborating entities of the study.

| | ITEM | COST |
|---|---|---|
| | CT Scans | 0 € *(Provided by the Hospital Clínic)* |
| | MRI Scans | 0 € *(Provided by the Hospital Clínic)* |
| **Human Resources** | Educational Stage | 1000 € |
| | Developmental Stage | 3000 € |
| | Writing Stage | 2800 € |
| | Total Cost Student | **6800 €** |
| **Software** | StealthStation S8 Medtronic | 0 € (Provided by the Hospital Clínic) |
| | MATLAB | University of Barcelona license |
| **Hardware** | StealthStation S8 Medtronic | 0 € *(Provided by the Hospital Clínic)* |
| | Private Computer | 1300 € |

| | |
|---|---|
| TOTAL COST | **8100 €** |

**Table 12.** Total budget, specified by activity, of the project

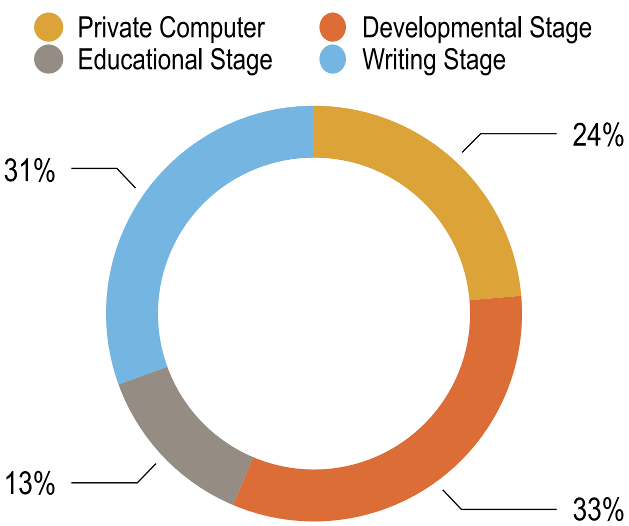


**Figure 27.** Cost divided per specific activity

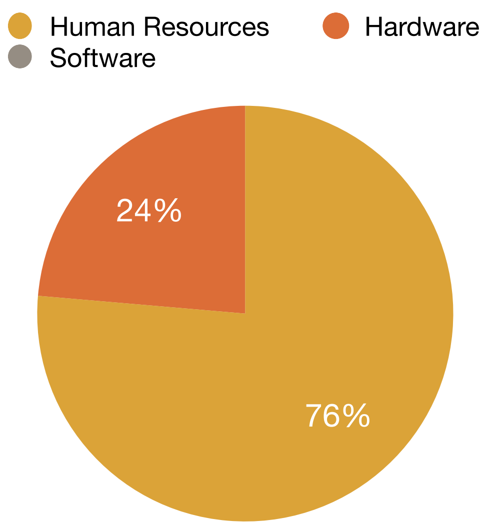


**Figure 28.** Cost divided per section: Human Resources, Software and Hardware

# 10. PROJECT IMPLEMENTATION SCHEDULE

## 10.1. GANTT DIAGRAM

The methodology followed the whole course of the project to obtain the results has been detailed in a GANTT diagram shown in Figure 29.

The study has followed a fairly linear development, where all tasks have been done sequentially. Nonetheless, the stage of writing the work began from the beginning and has been alternating with all other tasks.

Firstly, in the educational stage, a literature review of three months was accomplished in order to obtain sufficient knowledge to understand brain anatomy and physiology as well as PD. On account of this literature search, the author was able to understand the surgical procedure and different studies were analysed where a study of the error in STN-DBS interventions was performed. Subsequently, different DBS software was studied amidst the month of November as well as the obtaining of the images and their anonymization during December and January.

Later on, the developmental stage was initiated, with the co-registration and the acquisition of coordinates which were completed from mid-January to the first week of April to later compute the accuracy assessment in the course of April. While the necessary calculations and statistics were being performed, the author returned to intersperse them with the writing process.

Finally, once the relationship with the symptoms has been accomplished throughout the first weeks of May, the work has focused on finishing the report, the writing stage, with a delivery date of June 14 and, once delivered, the oral presentation was prepared knowing that it will be presented on June 21.

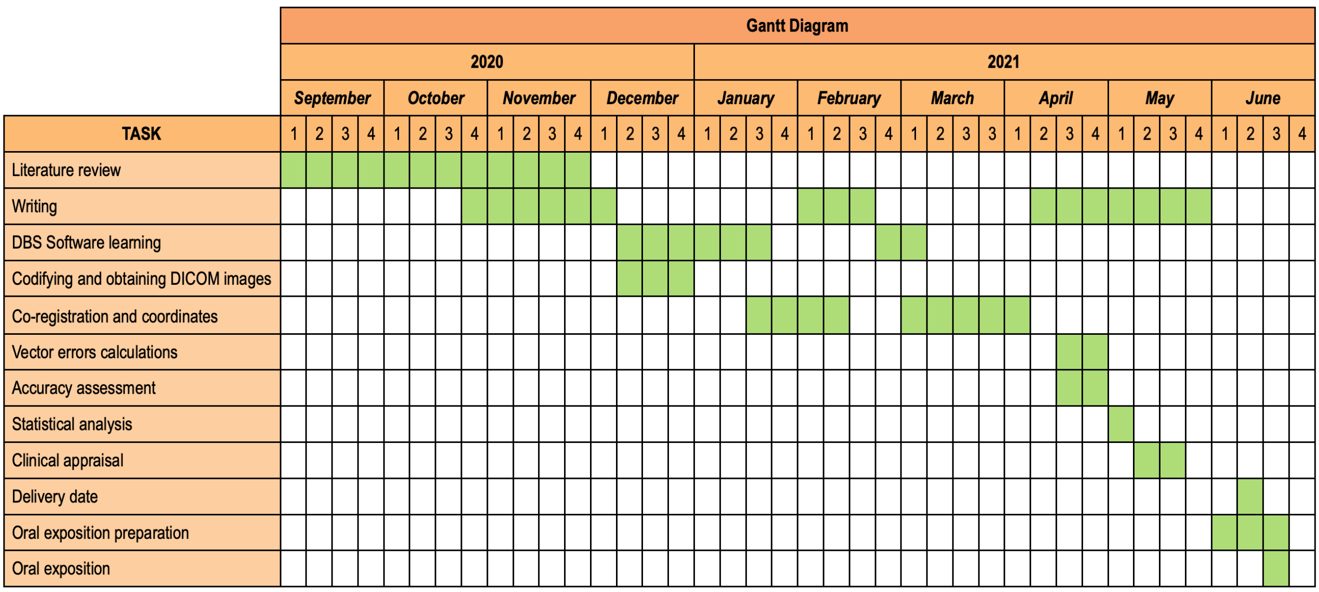


**Figure 29.** GANTT diagram followed the whole course of the study

# 11. CONCLUSIONS

To conclude, this project had the objective of validating the current technique of DBS electrode implantation accomplished in the Hospital Clínic of Barcelona by studying the accuracy of the placement using CT and MRI imaging and two different software: StealthStation S8 from Medtronic and MATLAB in patients with PD which electrodes stimulate the STN, as well as establishing a possible relationship between its symptomatology and provide objective arguments of a fully anaesthetised patient intervention.

Taking into account the whole population of the study, which has been 74 patients from 2015 to 2020, the absolute average accuracy in the right hemisphere has resulted to be 1.923 mm ± 1.107 whilst on the left hemisphere 2.364 mm ± 1.065. Consequently, in Leksell stereotactic system reviews have found out that the TE vary mostly from 3.00 mm to 1.33, whilst other systems such as the Neuromate Robot and i-MRI-guided system present a TE which is lower than 1 mm. In the case of the Hospital Clínic, the results are indeed consistent and statistically significant, nonetheless, other procedures could be adopted to perform the intervention to try to reduce TE as much as possible, such as a robotic arm.

On the other hand, it has been found that when an electrode has deviated from the expected target, it is explanted and relocated, or even the entire DBS system is replaced. Therefore, it has also been verified that there is a clinic related to the proper functioning of the system and that this is directly related to the position of the electrodes and, therefore, also to the accuracy. Nevertheless, it should be recalled that this intervention provides very favourable results for patients, with a considerable reduction in their motor symptoms if the type III UPDRS scale is taken into consideration. Hence, the objective involving the intervention's validation has been correctly accomplished.

Additionally, the image-guided and image-verified technique has been verified for having good accuracy while having the patient completely anaesthetised during the whole procedure, fulfilling the second and the third objective of the study. Thanks to this methodology, moving away from the MER-guided surgery, the patient can be asleep and would not have to withdraw his medication, thence relieving the preoperative anxiety he could be suffering from.

For the time being, in the majority of hospitals in Catalonia, the procedure is still being realised using the MER technique, resulting in a more extensive and longer surgery. Therefore, in the case of Parkinson's patients with STN stimulation, STN-DBS can be performed with reliable accuracy and offering remarkably results to the patient.

With regard to the limitations that have appeared in the work, the temporary limitation must be emphasised, since being a final degree project there is stipulated delivery date. Conversely, a more complete validation was desired with the study of the error of the trajectory and the deviations concerning the point of entry, however, it was not possible to execute since the necessary data had been erased. Even so, the considerable error, which is the one regarding the target (STN), has been successfully computed and analysed throughout the project.

Finally, to conclude, it is considerable to highlight the importance of technology, as well as biomedical engineering, in the field of neurosurgery. Communication between engineers and doctors or surgeons enables biomedical engineers to identify real problems during surgical interventions and to think of solutions to those issues. It is essential to bet on the use of biomedical engineers in operating rooms, as well as hospitals, to evolve and implement new technologies for diagnosis, treatment or even to improve surgical techniques. Medicine is certainly a field that is evolving more slowly than the rest, but it has the opportunity to take advantage of technological advances including robotics or artificial intelligence, and implement them on a day-to-day basis to facilitate procedures, alongside improving and making the patient's stay in the hospital more comfortable. On account of this, little by little biomedical engineers will be introduced even more into health systems to improve and help doctors to treat patients, and their presence will increase in the following years to come.

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# ANNEXES

## Patient's AC-PC Coordinates

| Patients | X right (mm) | Y right (mm) | Z right (mm) | X left (mm) | Y left (mm) | Z left (mm) |
|---|---|---|---|---|---|---|
| 3 | 13.28 | -1.1 | -4.31 | -12.88 | 0.55 | -5.21 |
| 4 | 11.03 | -2 | -4.45 | -10.24 | -2 | -5 |
| 6 | 12.84 | -2.66 | -4 | -11.22 | -2.66 | -4 |
| 7 | 11.55 | -1.58 | -4 | -10.87 | -1.02 | -4 |
| 8 | 12.8 | -2.95 | -4 | -11.6 | -2.5 | -4 |
| 9 | 10.07 | -2.4 | -4 | -10.14 | -2.21 | -4 |
| 10 | 12 | -2 | -4 | -12.69 | -2 | -4 |
| 11 | 10.14 | -1 | -4 | -10.34 | -1 | -4 |
| 12 | 11.37 | -4.82 | -4 | -11.9 | -2 | -4 |
| 13 | 10.46 | -3.3 | -4 | -10.46 | -2.4 | -4 |
| 14 | 10.34 | -2.5 | -4 | -10.62 | -2.27 | -4 |
| 15 | 11.4 | -1 | -4 | -11.14 | -0.45 | -4 |
| 18 | 9.34 | -3.54 | -4 | -9.8 | -2.28 | -4 |
| 20 | 10.77 | -0.53 | -4 | -10.23 | -1.67 | -4 |
| 21 | 11 | -2.9 | -4 | -9.24 | -2.55 | -4 |
| 22 | 10.57 | -2.77 | -3.28 | -11.11 | -1.79 | -2.19 |
| 23 | 12.16 | -2.76 | -4 | -12.3 | -0.55 | -3.75 |
| 24 | 15.24 | -3.93 | 1.37 | -11.92 | -4.39 | 2.13 |
| 25 | 11.43 | -4.05 | -4 | -9.12 | -2.5 | -4 |
| 28 | 11.16 | -2 | -4 | -11.58 | -2.63 | -4 |
| 30 | 11.85 | -0.9 | -4 | -9.62 | -2.21 | -4 |
| 31 | 12 | -4 | -4 | -10.6 | -2.63 | -4.43 |
| 32 | 11.52 | -2.32 | -4 | -11.68 | -2.69 | -4 |
| 33 | 11.47 | -1.5 | -4 | -9.43 | -2.9 | -4 |
| 35 | 11.26 | -6.29 | -4 | -12.33 | -4.66 | -3 |
| 36 | 13.35 | -4 | -2.33 | -12.02 | -3.95 | -2.52 |
| 37 | 12.38 | -1.03 | -4 | -10.14 | -2.6 | -4 |
| 38 | 10.82 | -1.93 | -4 | -10.92 | -2 | -4 |
| 39 | 12.5 | -2.05 | -4 | -10.47 | -3 | -4 |
| 40 | 12 | -4 | -4 | -11.78 | -4.28 | -4.12 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **41** | 10 | -1.63 | -4 | -9.5 | -2.2 | -4.2 |
| **42** | 10.28 | -1.5 | -3.63 | -9.59 | -2.14 | -3.5 |
| **43** | 10 | -3.52 | -4.33 | -9.29 | -2.77 | -4.28 |
| **44** | 10.62 | -4.85 | -4 | -10.03 | -5.12 | -4.28 |
| **45** | 12.67 | -0.18 | -3.1 | -9.81 | -2.75 | -4.12 |
| **46** | 12.19 | -1.89 | -4 | -9.69 | -3.7 | -4 |
| **47** | 11.67 | -0.95 | -4 | -11.67 | -0.95 | -4 |
| **48** | 12.93 | -1.95 | -4 | -9.88 | -3.41 | -4 |
| **50** | 11.88 | -1.65 | -4 | -9.32 | -2 | -4 |
| **51** | 12.8 | -1.4 | -4 | -10.54 | -2.1 | -4 |
| **52** | 11.6 | -2.31 | -4 | -11.58 | -2.62 | -4 |
| **53** | 12 | -4 | -4 | -11 | -3 | -4 |
| **54** | 13.5 | -4.4 | -1.37 | -12.9 | -4.04 | -1.41 |
| **55** | 12.9 | -1.4 | -3.8 | -12.54 | -1.21 | -3.76 |
| **56** | 12 | -4 | -4 | -12 | -4 | -4 |
| **57** | 9.95 | -3.6 | -4.22 | -7.24 | -5.39 | -4 |
| **58** | 11.04 | -3.68 | -3.92 | -12 | -4 | -4 |
| **59** | 11.83 | -0.61 | -4 | -10.67 | -2.1 | -4 |
| **60** | 10.25 | -4.24 | -3.46 | -12.32 | -3.71 | -2.51 |
| **62** | 12 | -4 | -4 | -12.62 | -3.96 | -4 |
| **65** | 12 | -4 | -4 | -12.73 | -3.45 | -4 |
| **66** | 12 | -3 | -4 | -11.45 | -3 | -4 |
| **67** | 12.46 | -3.5 | -4 | -10 | -2.5 | -4 |
| **68** | 11 | -2.9 | -3.9 | -12.06 | -3 | -3.95 |
| **69** | 12 | -4 | -4 | -11.16 | -3 | -4 |
| **70** | 11 | -2.5 | -4 | -9.5 | -3.06 | -4 |
| **72** | 12 | -4 | -4 | -12.25 | -2 | -4.11 |
| **73** | 10.26 | -4 | -3.66 | -9.5 | -4 | -4 |
| **74** | 11.41 | -3 | -4 | -8.74 | -3.5 | -4 |
| **75** | 12 | -1.9 | -4.17 | -12.38 | -1.63 | -3.87 |
| **76** | 10 | -3.6 | -4 | -8 | -4 | -4 |
| **77** | 10.19 | -3 | -4 | -11 | -4 | -4 |
| **78** | 10.57 | -2 | -3 | -10.51 | -3 | -4 |
| **79** | 12 | -1 | -4 | -10 | -1 | -4 |
| **80** | 12.11 | -3.19 | -4 | -12 | -2 | -4.3 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **81** | 10.5 | -1.8 | -3.9 | -10 | -2 | -4.14 |
| **82** | 12.8 | 0.73 | -3.63 | -10 | 0.26 | -3.8 |
| **83** | 12 | -4 | -4 | -12 | -4 | -4 |
| **84** | 10.7 | -2 | -4 | -9.3 | -3.5 | -4 |
| **86** | 9.33 | -2.57 | -4.03 | -9.58 | -0.54 | -3.77 |
| **87** | 11.73 | -2.71 | -3.02 | -12.59 | -0.89 | -3.72 |
| **89** | 10.9 | -4 | -3.9 | -10 | -4 | -4 |
| **90** | 9.42 | -1.12 | -4.17 | -9.35 | -1.14 | -4 |
| **92** | 11.87 | -3.16 | -4.43 | -10.31 | -3 | -4 |
| **93** | 10.15 | -3.36 | -4 | -10.13 | -3.18 | -4 |
| **94** | 12 | -4 | -4 | -10.13 | -4.3 | -4 |

## MATLAB code to calculate the vector error

```
%Vector Error
%Accuracy Assessment
target = csvread("target_points_2.csv",1,0);

%Accuracy Assessment - Right STN
%Atlas AC-PC coordinates
x0_r = 12;
y0_r = -4;
z0_r = -4;

for i = 1:1:76
    data_def_x = target(:,i+1); %All x values
    data_def_y = target(:,i+2); %All y values
    data_def_z = target(:,i+3); %All z values
    d_right = sqrt((data_def_x-x0_r).^2+(data_def_y-
y0_r).^2+(data_def_z-z0_r).^2)
end

%Accuracy Assessment - Left STN
%Atlas AC-PC coordinates
x0_l = -12;
y0_l = -4;
z0_l = -4;
```

```
for i = 1:1:76
    data_def_x = target(:,i+4); %All x values
    data_def_y = target(:,i+5); %All y values
    data_def_z = target(:,i+6); %All z values
    d_left = sqrt((data_def_x-x0_l).^2+(data_def_y-
y0_l).^2+(data_def_z-z0_l).^2)
end
```

### MATLAB code to accomplish the statistical analysis

```
%Statistical Appraisal
clc
clear all

distance = linspace(0,76,76);
v_error = csvread("vectorerror.csv",1,0);

%Average errors
mean_right = mean(v_error(:,1));
mean_left = mean(v_error(:,2));

%Standard deviation
sd_right = std(v_error(:,1));
sd_left = std(v_error(:,2));

%Paired Student T-Test
[h,p] = ttest(v_error(:,1),v_error(:,2));
h
p

%Colour
c = "r"

%Plot representation
scatter(v_error(:,2),v_error(:,4), c);
title('Left Vector Error')
xlabel('Vector Error')
ylabel("Distance from AC-PC")
```